Sustainable Methodology for the Synthesis of Amides, Esters and Polypropionate Fragments

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Sustainable Methodology for the Synthesis of Amides, Esters and Polypropionate Fragments

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Centre for Sustainable Chemical Technologies

Department of Chemistry

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Abstract

This thesis presents research into the development of sustainable methodology for the synthesis of amides, esters and polypropionate fragments. As well as a literature review of efficient natural product synthesis.

Acylals are a known class of reagent that have been utilized within literature for a wide range of synthetic methodologies. Herein we present acylals as new highly active reagents for the *N*-/*O*-acylation of amines and alcohol nucleophiles for the synthesis of a range of formamides, acetamides, formate esters and acetate esters. It has been demonstrated that a range of acyl groups can be transferred including short and long chain alkyls, acryloyl, benzoyl, phenyl acetyl and biologically important trifluoroacetyl group, thus enabling the synthesis of a range of benzylamides and esters. These acylation reagents have also been shown to demonstrate inherent *N*-/*O*- selectivity towards the amine and alcohol groups of serine methyl ester.

The scope and limitations of these reagents of the use of acylals has been investigated through the *N*-formylation of a range of unprotected amino acids, and for the synthesis of the biologically important tripeptide f-MLP. As well as the acylation/formylation of the ω-amino residue of a lysine residue within a decapeptide. Finally, it has also been demonstrated that a simple switch in pH from basic to acidic conditions for diols can change from *O*-acylation to acetal formation.

The synthesis of enantiomerically enriched dihydropyrans from the heteo-Diels-Alder reaction of 1-alkoxy dienes and ethyl glyoxalate has been presented. A series of stereoselective derivatisation reactions were developed including, hydroboration, hydrogenation, epoxidation, dihydroxylation and epimerization which procced with stereoselectivity to afford a range of complex enantiomerically enriched polypropionate based building blocks, which are ideally suited for the synthesis of polyketide natural products through a “plug and play” approach. Chemistry has also been presented which makes use of the orthogonally addressable synthetic handles of the pyran building blocks. Utilization of either the masked aldehyde character or the ester functionality present allows for further elaboration of the pyran building blocks by selectively introducing new functionality.

Acknowledgements

First and foremost I would like to thanks Prof. Steve Bull who has provided great advice and ideas throughout my PhD. He has provided me with unbelievable opportunities over the years and for those I will be forever grateful, I look forward to his continued support and friendship in the future. Even if it does mean I have to keep letting him beat me at pool on a regular basis.

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I would like to thank my second supervisors Dr Matthew Jones and Dr Pawel Plucinski, whose help was always available if I needed it. I would also like to extend my thanks to John Lowe for all his NMR help, Dr Heather Parker and Dr Rhodri Owens for their help with the GC, Georgina Gregory for help with DFT calculations and Dr Ruth Webster for allowing me to use her glovebox.

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Contents

Abbreviations

Ac	Acetyl
α	Alpha
Acm	Acetamidomethyl
app	Apparent
Ar	Aryl
β	Beta
BINAP	(1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
BINOL	1,1′-Bi(2-naphthol)
br	Broad
^{13}C NMR	Carbon 13 Nuclear Magnetic Resonance
J	Coupling constant
^{o}C	Degrees Centigrade
δ	Delta, Chemical shift
CAR	Conformational activity relastionship
$CDCl_3$	Deuterated Chloroform
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
CH_2Cl_2	Dichloromethane
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DEBS	Deoxyerythronolide B synthase
DFT	Density functional theory
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBALH	Diisobutyl aluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
eq	Equivalents
Et	Ethyl
f-MLP	*N*-formylmethionyl-leucyl-phenylalanine
FGI	Functional group interconversion
GC	Gas chromatography
g	Grams
H_2O_2	Hydrogen peroxide
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HDA	Hetero-Diels-Alder
Hz	Hertz
HTP	High through put
HOMO	Highest occupied molecular orbital
h	Hours
IAC	Intramolecular acylal cyclisation
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
LA	Lewis acid
LDA	Lithium diisopropylamine
LHMDS	Lithium bis(trimethylsilyl)amide
$LiAlH_4$	Lithium aluminium hydride
LUMO	Lowest unoccupied molecular orbital
m/z	Mass to charge ratio
MHz	Megahertz

Me	Methyl
PMB	4-methoxy benzylether
***m*CPBA**	*meta*-Chloroperbenzoic acid
Min	Minutes
mL	Millilitres
mmol	Millimoles
m	Multiplet
mol%	Mole percent
Ms/Mesyl	Methanesulfonyl
nm	Nanometres
NBS	*N*-bromosuccinimide
NCL	Native chemical ligation
nOe	Nuclear Overhauser Effect
NADH	Nicotinamide adenine dinucleotide
NBS	*N*-Bromosuccinimide
nBuLi	n-Butyl lithium
N_3	Azide
NHK	Nozaki-Hiyama-Kishi
NICE	National institute for clinical excellence
NMR	Nuclear Magnetic Resonance
NMM	*N*-Methylmorpholine
NMIM	*N*-Methyl imidazole
NMO	*N*-Morpholine-N-oxide
nuc	Nucleophile
PKC	Protein kinase C
PKS	Polyketide synthase
$POCl_3$	Phosphorus(V) oxide chloride
ppm	Parts Per Million
Ph	Phenyl
PS	Polymer supported
Py	Pyridine
PPTS	Pyridinium *para*-toluenesulfonate
q	Quartet
R	Unspecified generic group
RCM	Ring closing metathesis
rt	Room temperature
s	Singlet
SAR	Structural activity relationship
SMB	Simulated moving bed
t	Tertiary
TBAF	Tetra-n-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TCAA	Trichloroacetic anhydride
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TES	Triethyl silyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TCDI	Thiocarbonyl diimidazole
TRAM	Triarylmethane
t	Triplet

Ts/Tosyl	*para*-Toluenesulfonyl
UV	Ultra violet

1.0 Use of Acylals as *N*- and *O*- Formylation and Acylation Agents

1.1 Introduction

Acylation reactions, and in particular acetylation reactions, are some of the most significant and widely used transformations in organic synthesis.[1-5] The amide bond is ubiquitous throughout nature (e.g. peptides, proteins, etc...) and is found in many pharmaceutically active molecules (Figure 1), resulting in the *N*-acylation of amines and *O*-acylation of alcohols being two of the most widely utilized reactions in drug and agrochemical synthesis.[1, 6, 7]

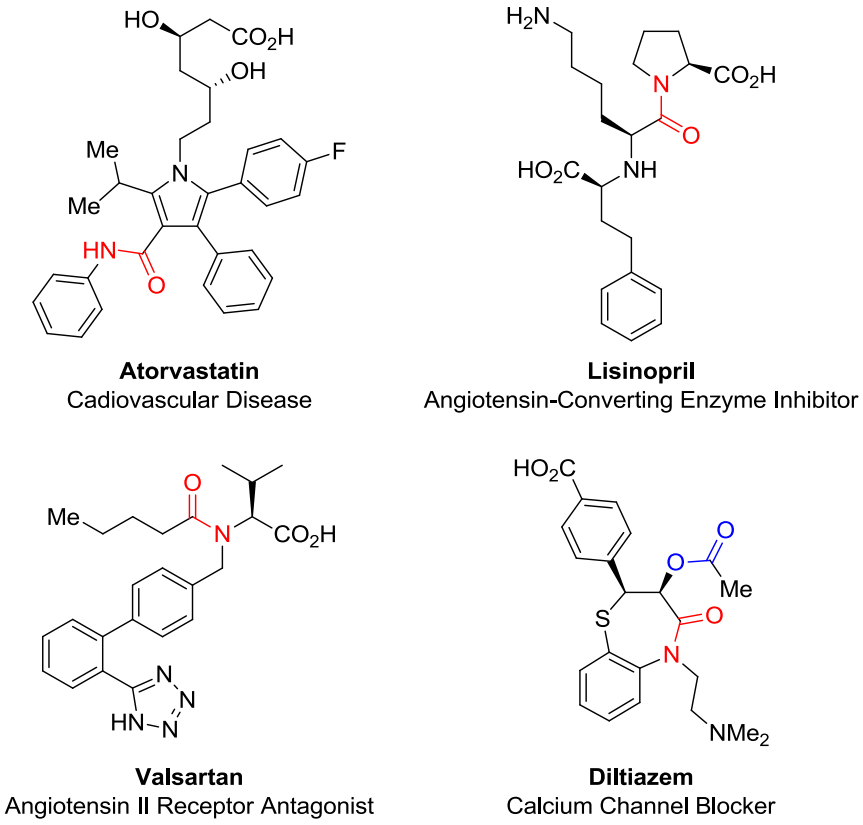
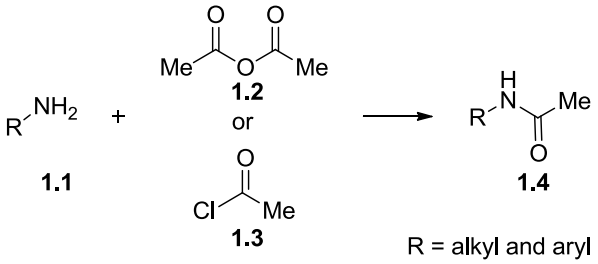


Figure 1. Examples of top selling drugs containing amide or ester acyl groups.[7]

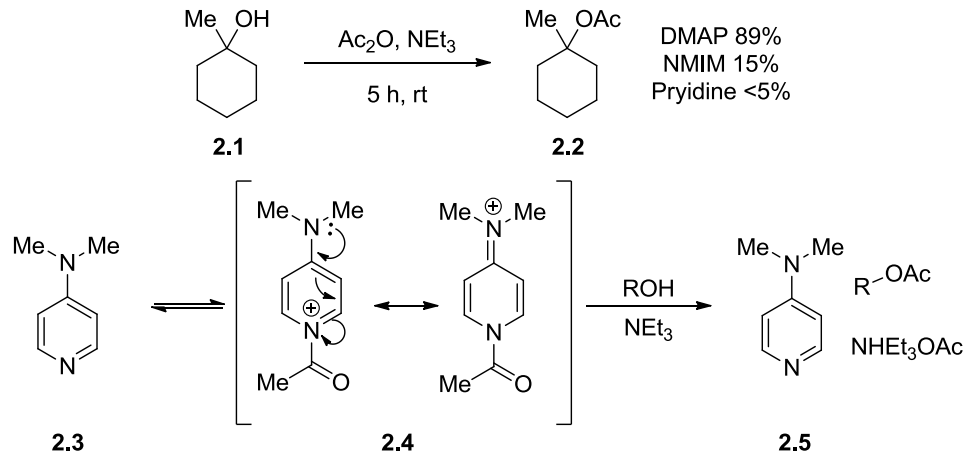
1.2 Acylation Strategies

Traditionally, *N*-acylation reactions are carried out utilizing carboxylic acid derivatives, namely acid anhydrides **1.2** and acyl chlorides **1.3**. Variations of these approaches form the basis of the majority of synthetic acylation reactions (Scheme 1).[8]



Scheme 1. Traditional methods of carrying out *N*-acylation chemistry.

Modern variations on this theme can be performed in a range of organic solvents and often utilize acyl transfer agents such as dimethylaminopyridine (DMAP) and its derivatives, as well as Lewis acid catalysts.[9-11] DMAP **2.3** is able to act as a nucleophilic organocatalyst, which attacks an anhydride (or acyl chloride) to generate an activated acyl transfer agent (e.g. acetylpyridinium **2.4**) which is then more reactive towards amine and alcohol nucleophiles, thus facilitating the formation of amides and esters. For example the acylation of sterically hindered methylcyclohexanol **2.1** with acetic anhydride to give methylcyclohexyl acetate **2.2** was explored by Goe *et al.*, with three additives tested for this reaction. DMAP performed best giving an 89% yield, of the desired ester **2.2**, whereas *N*-methyl imidazole (NMIM) and pyridine gave only 15% and <5% yields respectively. This increase in yield is attributed to the ability of DMAP to act as a nucleophilic catalyst, which generates a resonance stabilized reactive intermediate *in situ* (Scheme 2).[10]



Scheme 2. Use of DMAP as an acyl transfer catalysts.[10]

However, there are a number of problems associated with the use of acyl chlorides and anhydrides for acylation reactions. For example; reaction of amines with acyl chlorides can be highly exothermic, while anhydrides can form side products (e.g. imides) when reacted with primary amines.[12] Acyl chlorides and anhydrides are also known to be moisture sensitive, with the high reactivity of acid chlorides meaning they are potentially liable to decomposition and competing side reactions.[1-4] It is worth noting as well, that while anhydrides and acyl chlorides are moisture sensitive, in some cases they have been shown to be stable enough to allow the reaction to be performed in aqueous media.[13]

Some of these disadvantages have been alleviated through the direct use of carboxylic acids as acyl sources, which is of particular interest for peptide synthesis. Whilst an obvious solution is to covert the acid to an acyl chloride *in situ*, this approach is only really applicable to relatively simple substrates, with problems often encountered when more complex substrates are used. Consequently, a whole suite of coupling reagents have been developed that activate carboxylic acids towards nucleophilic addition of amines and alcohols. Coupling reagents based on carbodiimide (DCC), *N*-acylimidazoles (CDI), phosphonium salts (BOP) and guanidinium salts (HATU) are regularly used in peptide synthesis, which afford excellent yields for amide bond formation and crucially without eveidnece of any racemization (Figure 2).[7] However, the use of these coupling reagents can be considered to be expensive and wasteful, since they generate stoichiometric amount of by-products.

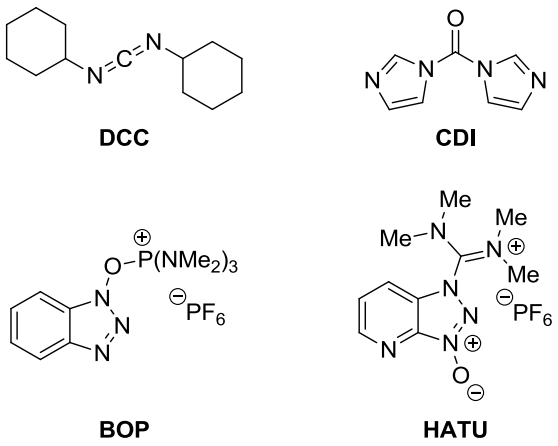
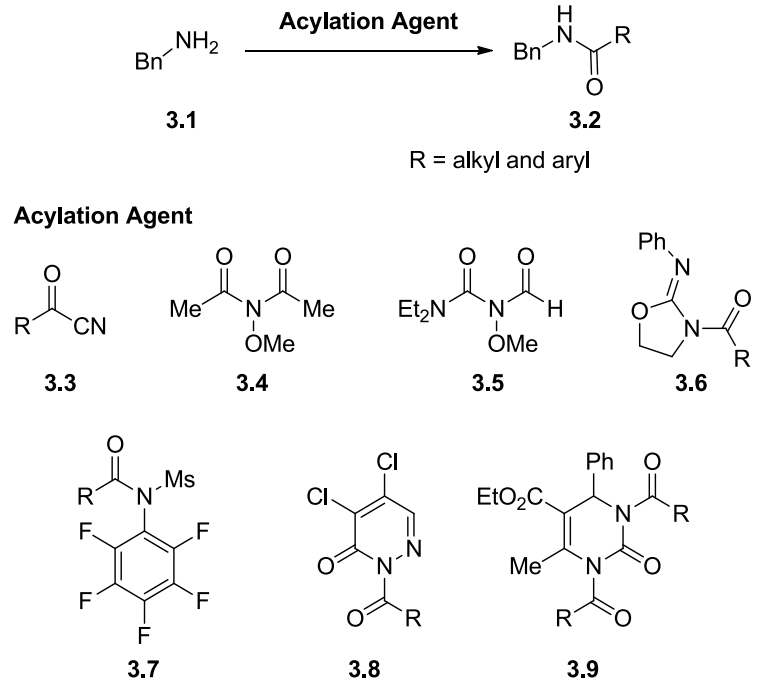


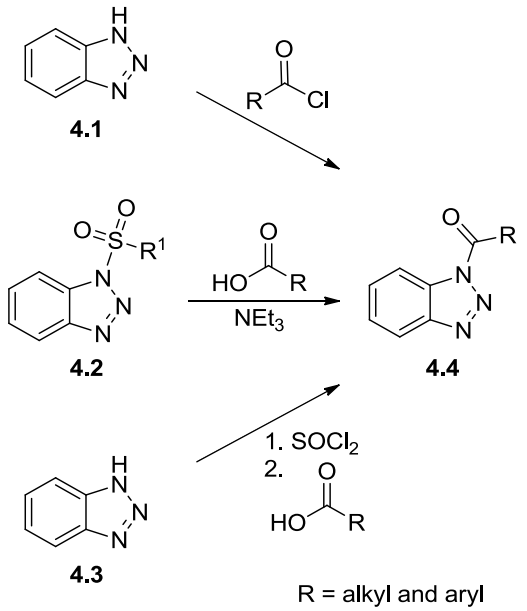
Figure 2. Examples of common peptide coupling reagents.

In response to this, a range of acylation reagents have been developed in the literature that act directly as acyl transfer agents, rather than relying on the activation of a starting material or intermediate *in situ* (Scheme 3). One of the first acylation reagents were acyl cyanides **3.3**, which were first reported as an alternative reactant to acyl chlorides in 1954.[14] More recently, Murahashi and Naota have reported an efficient acyl cyanide synthesis utilizing a ruthenium catalyzed oxidation of the corresponding cyanohydrins using *tert*-butylhydroperoxide as an oxidant.[15, 16] These acyl cyanides were shown to be highly chemoselective with only *N*-acylation observed for a number of amino alcohol substrates. Kikugawa and co-workers have demonstrated the use of *N*-methoxydiacetate **3.4** as a highly selective *N*-acylation reagent, that selectively acylated primary amines over both secondary amines and alcohols.[17] This was developed into the bench stable *N*-diethylcarbonyl-*N*-methoxyformamide **3.5**, which acts as a selective *N*-formylating reagent. *N*-acyl-2-phenylimino-oxazolidines **3.6** developed by the Kim group have been shown to be highly active acylation agents, demonstrating high yields with a range of primary and secondary amines, as well as amino alcohols.[18] The Murakami group have developed a range of acylation agents based on substituted anilines, including *N*-acyl-*N*-(perfluorophenyl)methanesulfonamides **3.7**, which have been shown to demonstrate high activity towards primary and secondary amines.[19] Yoon *et al.* have shown that air stable 2-acyl-4,5-dichloropyridazin-3-ones **3.8** are effective *N*-acylation agents, with the parent 4,5-dichloropyridazin-3-one by-product potentially being isolated and recycled.[20] This potentially reduces the impact caused through the use of stoichiometric reagents. More recently, Singh *et al.* have shown that N^1-N^2-diacyl-3,4-dihydropyrimidin-2(1H)-ones **3.9** are affective acylation agents for a range of substrates, including ammonia, primary and secondary amines.[21]



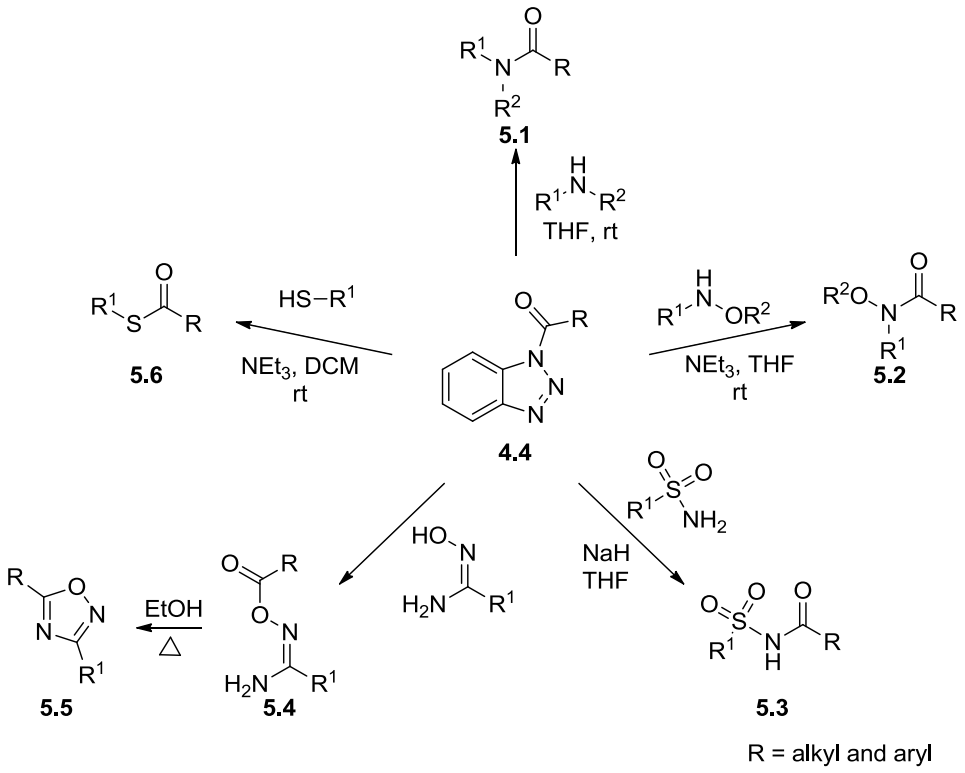
Scheme 3. Representative range of effective acylating agents.

Katritzky and co-workers have extensively researched the use of *N*-acylbenzotriazoles **4.4** as stoichiometric acylating reagents. The group have synthesised an impressive number of crystalline and bench stable *N*-acylbenzotriazoles **4.4** over the past 20 years, and have used them to acylate a wide range of different nucleophiles. Their original synthesis was performed using benzotriazole **4.1** and acyl chlorides, or through the reaction of carboxylic acids with *N*-sulfonylbenzotriazoles **4.2**. These reagents were then developed further to allow the direct reaction of carboxylic acids and benzotriazole, facilitated by thionyl chloride. This modification allowed for the use of potentially unstable acyl chlorides as the acyl donor (Scheme 4).[22-25]



Scheme 4. Synthesis of *N*-acylbenzotriazoles

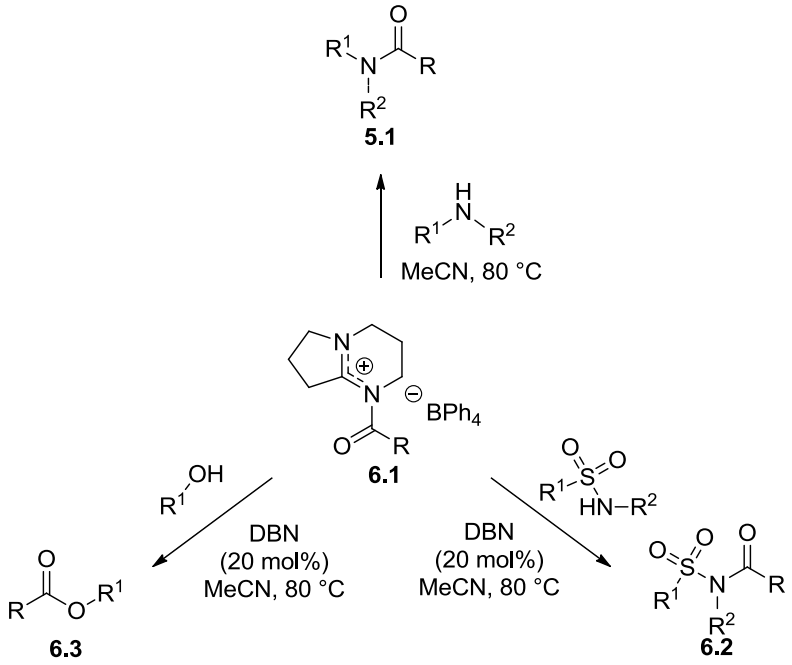
Summarising their extensive results, *N*-acylbenzotriazole **4.4** is active against the range of nucleophiles shown in Scheme 5. As well as the synthesis of amides **5.1**,[12] *N*-acylbenzotriazoles react with a range of *N*-substituted hydroxylamines for the synthesis of Weinreb amides **5.2**.[26, 27] *N*-acylsulphonamides **5.3**, which represent a common motif in many drug like molecules, can also be accessed through the use of *N*-acylbenzotriazoles.[28] *N*-acylbenzotriazoles **4.4** can also act as *O*-acylation agents. For example, they react with amidoximes in ethanol at rt to form *O*-acylated amidoximes **5.4**, which upon heating, cyclise to form the corresponding 1,2,4-oxadiazoles **5.5**.[29] Their effectiveness as *S*-acylation agents has also being demonstrated through the synthesis of a range of thioesters **5.6** (Scheme 5).[30]



Scheme 5. Selective examples of the utility of *N*-acylbenzotriazole **4.4** as a versatile acylating agent

Bull and co-workers have recently demonstrated *N*-acyl 1,5-diazobicylco[4.3.0]non-5-ene (DBN) tetraphenylborate salts **6.1** as acylation reagents. These salts are air stable crystalline solids, which are readily synthesised from DBN and the corresponding acyl chloride, allowing for easy storage and increased shelf life when compared with the corresponding acyl chlorides or acid anhydrides.[1] These DBN salts **6.1** have been shown to be active against a range of amines to give the corresponding amides **5.1**. Alcohols and sulphonamides can also be acylated to give the corresponding esters **6.3** and *N*-acyl sulphonamides **6.2** respectively (Scheme 6).[1, 2]

To summarize, while there are a number of acylation reagents and strategies, there is still scope to develop new methodologies that afford amide, ester and sulfonamide bonds, since they represent some of the most important functional groups in organic and medicinal chemistry.[5] Furthermore, there is still much demand for milder and racemization free reaction conditions, as well as the ability to improve the selectivity of acylation reactions (e.g. *N*-acylation vs *O*-acylation, reaction of 1° amine over 2° amine).

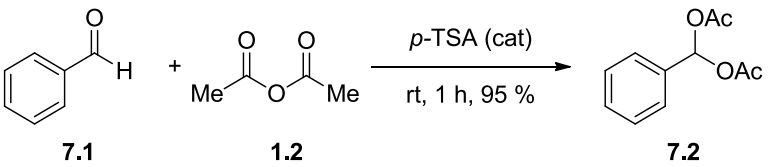


Scheme 6. *N*-acyl DBN BPh_4 salts as acylating agents

This chapter will now describe our investigations into the potential of using acylals as *N*- and *O*- acylation agents for amines and alcohols.

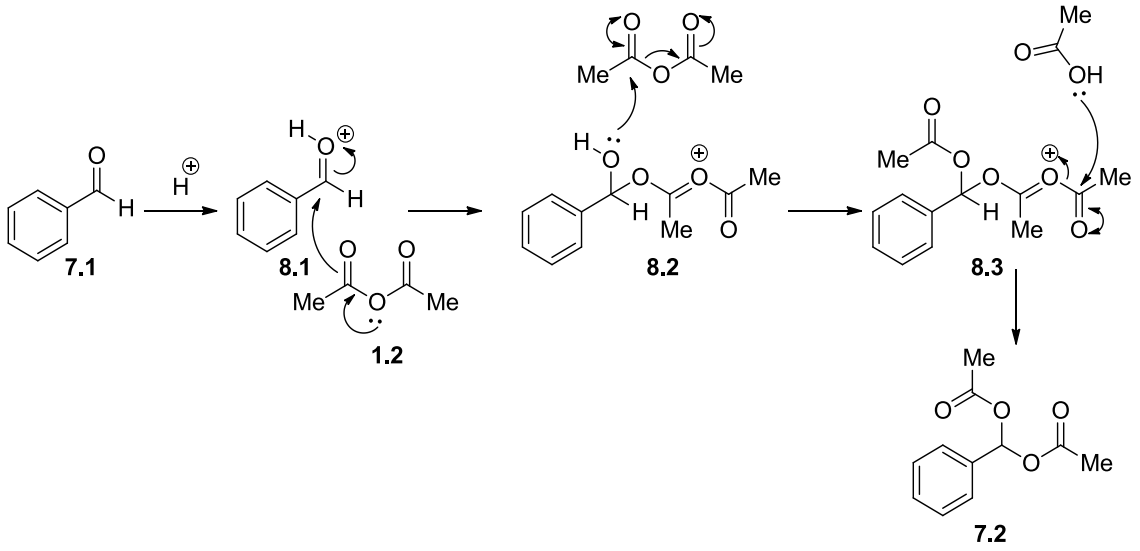
1.3 Phenylmethylene Diacetate as an Acylation Reagent

The known compound phenylmethylene diacetate **7.2**, can be readily synthesized from benzaldehyde **7.1** and acetic anhydride **1.2** using *para*-toluenesulfonic acid (*p*-TSA) as a Brønsted acid catalyst (Scheme 7). These class of compounds have been employed as reagents in a range of synthetic methodologies,[31] and are referred to as either *gem*-diacetates, or acylals.[32]



Scheme 7. Synthesis of phenylmethylene diacetate.

It is proposed that the mechanism of formation of acylal **7.2** proceeds *via* an intermolecular pathway, with the Brønsted acid first protonating benzaldehyde **7.1** to give oxonium **8.1**, which then allows for nucleophilic attack of acetic anhydride **1.2** at its carbonyl to afford hemiacetal **8.2**. A second anhydride equivalent is then able to acylate the alcohol group of this hemiacetal intermediate to afford acyl oxonium **8.3**. Nucleophilic attack of acetic acid then affords the observed phenylmethylene diacetate **7.2** (Scheme 8).[33, 34]

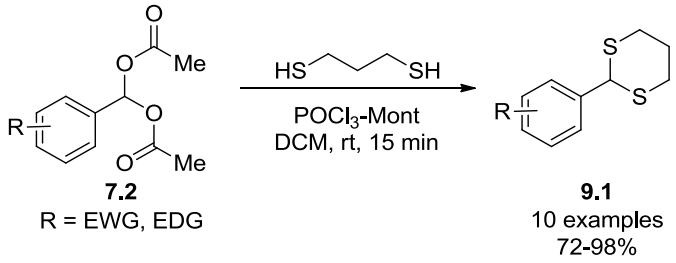


Scheme 8. Proposed mechanism for the formation of acylal **7.2**.

We envisaged that these type of acylals might be useful as selective acylating agents, and now briefly review the literature to summarize where they have been used presviously as versatile reagents for synthesis.

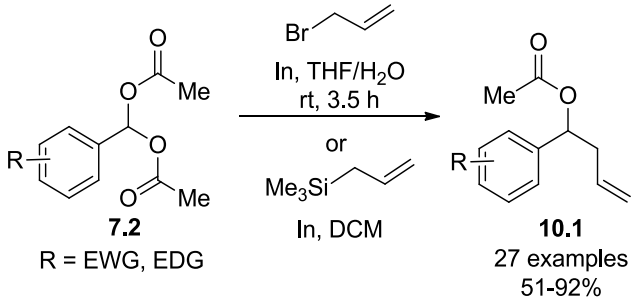
1.4 Synthetic Utility of Phenylmethylene Diacetate

Phenylmethylene diacetate **7.2** (or structural analogues) has been used as a reagent for a range of different synthetic methodologies, some of which will now be discussed in detail to highlight the versatility of this class of reagents. One use of acylals is as substrates for transdithioacetalization reactions to afford cyclic dithianes **9.1**.[35, 36] Exposure of acylal to dithiols under a range of mild acid catalyzed conditions affords cyclic thioacetates **9.1**, with the reaction procceding under relatively mild conditions with improved reactivity when compared to reaction of the parent aldehyde (Scheme 9).[35, 36]



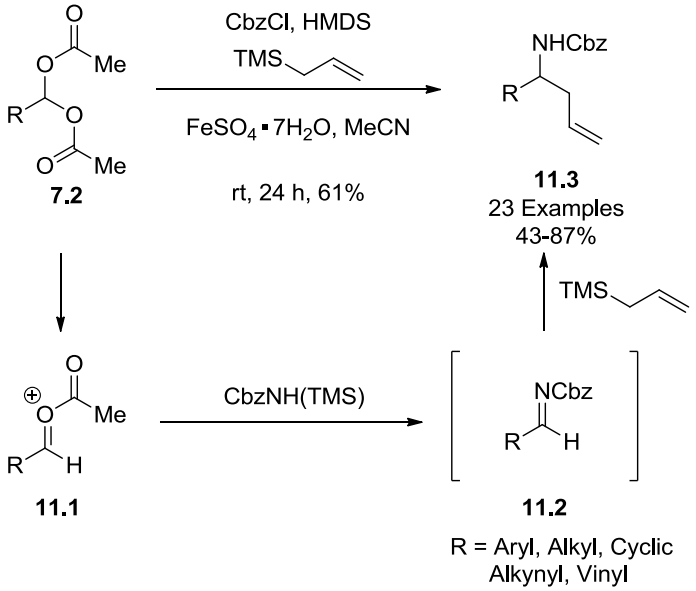
Scheme 9. Use of phenylmethylene diacetate **7.2** in transdithioacetalization reactions[35]

Acylals have also found application for the synthesis of allylic acetates, with variants of this reaction employing allyl silanes, allyl bromides or allyl samarium bromides as the allylating source.[37-39] For example, Yadav *et al.* have developed indium catalyzed allylation reactions of acylals utilizing either allyl bromides or allyl silanes, to afford a wide range of allylic acetates under relatively mild reaction conditions (Scheme 10).



Scheme 10. Indium catalysed allylation reaction of acylal **7.2**[37, 38]

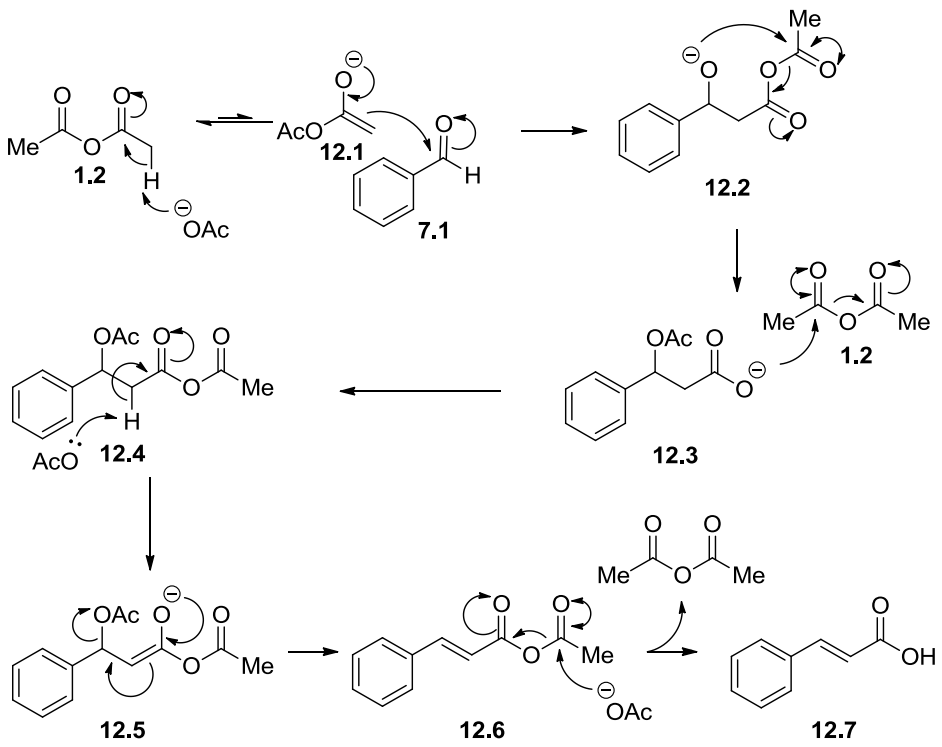
A further extension of this type of allylation methodology has been shown by Song *et al.* who demonstrated that phenylmethylene diacetate **7.2** could be applied for the synthesis of protected homoallylic amines **11.3**.[40] The reaction is proposed to proceed through iron catalysed reaction of CbzNHTMS with diacetate **7.2**, to afford immine intermediate **11.2**. A Cbz-TMS adduct is formed through reaction of Cbz-Cl and HMDS, *in situ*, which then reacts with an *in* situ formed acyl oxonium species **11.1** to generate the desired imine. This imine is then able to undergo nuclephilic attack of the allyl group to give the desired Cbz-protected homoallylic amine **11.3**.[40]



Scheme 11. Synthesis of protected homoallylic amines[40]

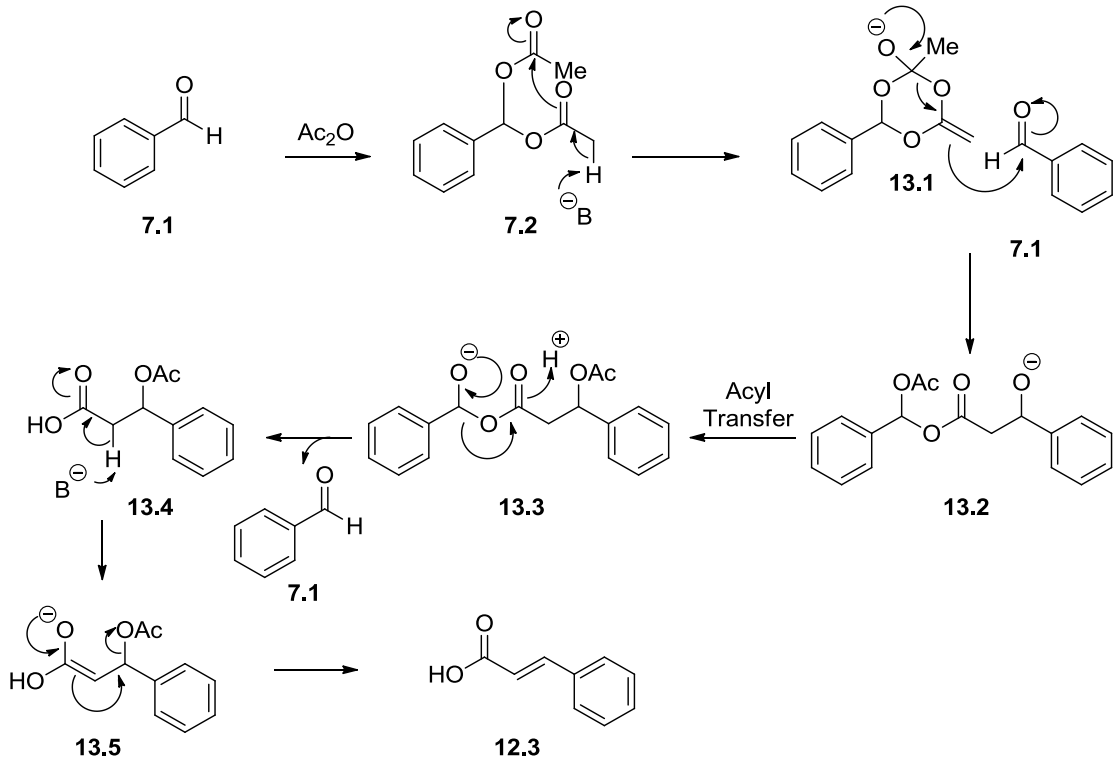
Acylals have recently been proposed as key intermediates in the Perkin condensation reaction for the synthesis of cinnamic acids, whereby benzaldehyde, acetic anhydride, potassium acetate, are reacted at 180 °C. The traditionally accepted mechanism for the Perkin reaction is proposed to proceed *via* formation of an anhydride enolate **12.1**, which is able to undergo nucleophilic attack at benzaldehyde **7.1** to afford the anhydride alkoxide **12.2**. Intramolecular acyl transfer then occurs to generate carbonate **12.3**, which then undergoes nucleophilic attack at a second equivalent of acetic anhydride **1.2** to give acetate **12.4**. E1cB elimination of acetate from **12.4**, followed by hydrolysis of anhydride **12.6** then affords the observed cinnamic acid **12.7** (Scheme 12).

However, it has been noted that the reaction conditions employed for the Perkin reaction are unlikely to generate enolate **12.1**, because a strong base is not present, with the mechanism proposed in Scheme 12 requiring that a weakly basic acetate ion function to generate the required enolate. Further evidence that the literature mechanism may be incorrect, is that the anhydride, when subjected to the reaction conditions in the absence of aldehyde remains stable. If the enolate **12.1** is formed under these conditions, then it is likely that is would rapidly fragment to afford a ketene under the high temperatures employed (Scheme 12).[41]



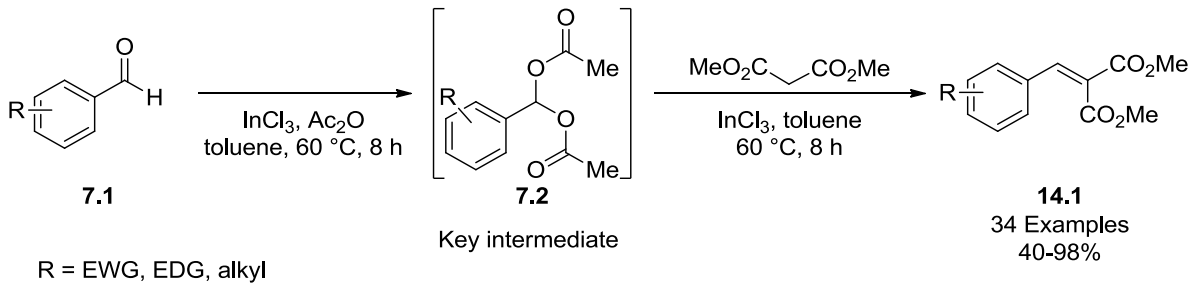
Scheme 12. Traditional mechanism proposed for the Perkin reaction

Chandrasekhar *et al.* proposed that the reaction proceeds *via* formation of an acylal intermediate, showing that the Perkin reaction proceeds when acylal **7.2** is used as a replacement substrate for benzaldehyde **7.1**. They propose that reaction of acylal **7.2** with base affords a cyclic orthoester **13.1**, which then undergoes nucleophilic attack at benzaldehyde **7.1** to afford alkoxide **13.2**, which then undergoes acyl transfer reaction to generate acetate **13.3** (intermolecular rather than intramolecular?). Elimination of benzaldehyde from **13.3** then occurs to afford carboxylic acid **13.4**, which then undergoes E1cB elimination of acetate to give the observed cinnamic acid **12.3** (Scheme 13).[41]



Scheme 13. Use of phenylmethylene diacetate as an alternative substrate in the Perkin reaction[41]

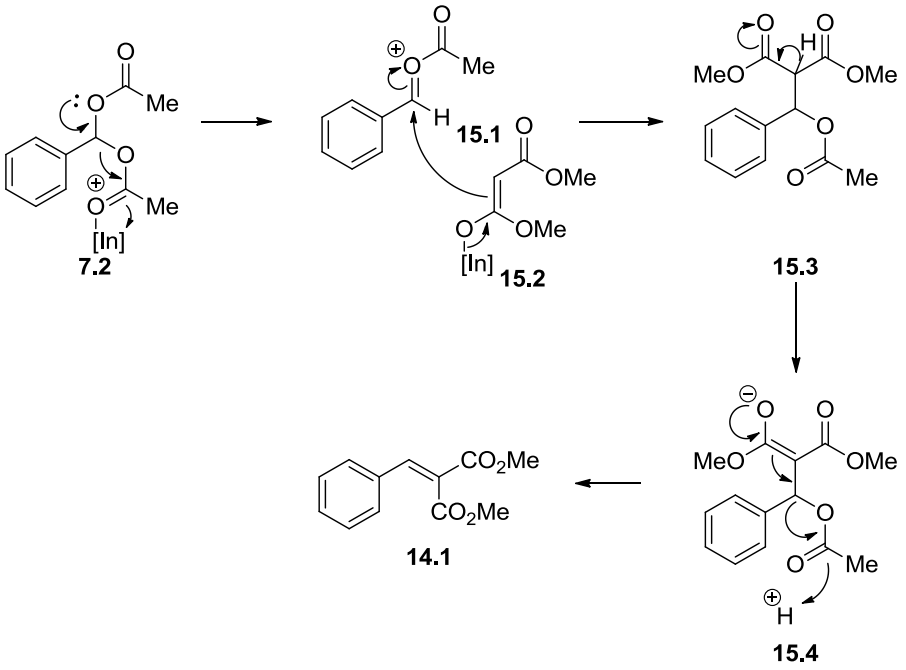
A recent publication by the Sakai group also identified acylal **7.2** as a key intermediate in their indium catalyzed Knoevenagel condensation of aldehydes with dimethyl malonate for the synthesis of α,β-unsaturated bis-esters **14.1** (Scheme 14).[42]



Scheme 14. Indium catalysed Knoevenagel condensation[42]

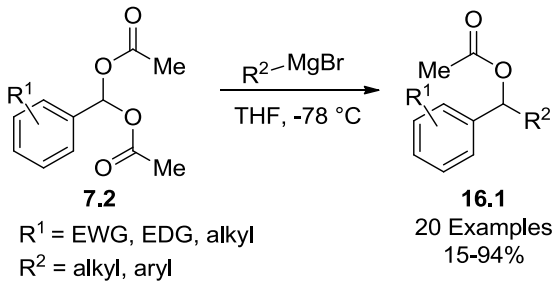
It is proposed that indium catalyzed reaction of benzaldehyde with acetic anhydride affords phenylmethylene diacetate **7.2** *in situ*, which then undergoes indium catalyzed

deacetylation to give acyl oxonium **15.1**. Oxonium **15.1** then reacts with an indium generated enolate **15.2** to afford tris-ester **15.3**, that then undergoes E1cB elimination to afford the desired α,β-unsaturated bis-ester **14.1** (Scheme 15).[42]



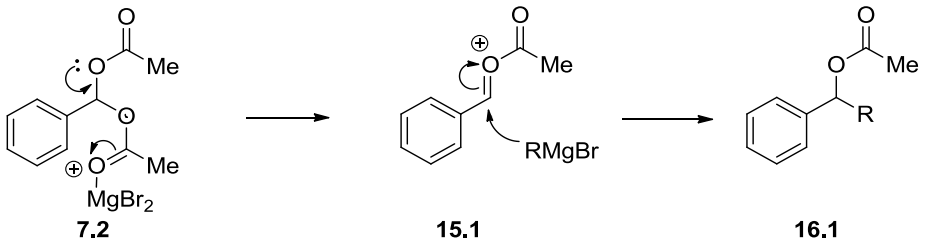
Scheme 15. Proposed mechanism for indium catalysed Knoevenagel condensation[42]

As well as these relatively recent examples of the synthetic utility of phenylmethylene diacetate **7.2**, Sandberg and Sydnes published an earlier series of work looking at the chemistry of acylals.[43-46] The first publication explored the reactivity of acylals towards Grignard and organolithium reagents, with the carbon nucleophile being able to selectively displace one of the acyl ester groups to afford a range of substituted esters **16.1** (Scheme 16).[43] It is interesting to note that acylals demonstrated greater reactivity towards Grignard reagents than aldehydes, which was established through a competition experiment between acylal **7.2** (R = *p*-OMe) and 4-methoxy benzaldehyde, and 0.5 equiv. of Grignard nucleophile, with only the acylal being consumed.[43]



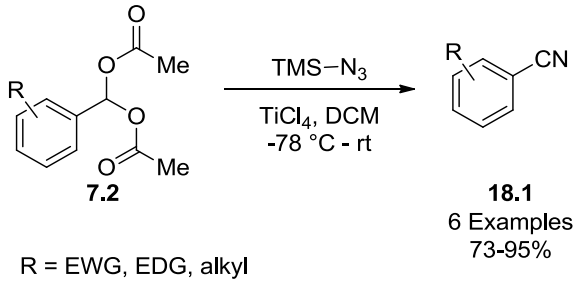
Scheme 16. Reaction of acylals with Grignard and organolithium reagents[43]

The mechanism is believed to proceed *via* formation of acyl oxonium **15.1** which is able to undergo nucleophilic attack of the Grignard reagent at the oxonium carbonyl to give the observed acetate ester **16.1** (Scheme 17).



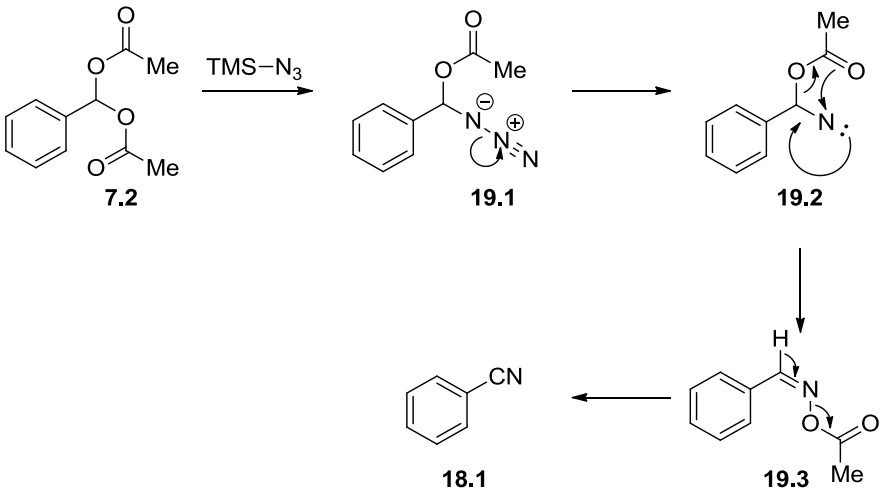
Scheme 17. Mechanism for the reaction of acylals with Grignard reagents.[43]

Their second report focused on reactivity of acylals towards azide species. In efforts originally aimed at performing azide substitution reactions of acylals, they found that reaction with TMS-N_3 (trimethylsilyl azide) in the presence of a Lewis acid catalyst (titanium(IV) chloride) led to the formation of nitriles **18.1** (Scheme 18).[44]



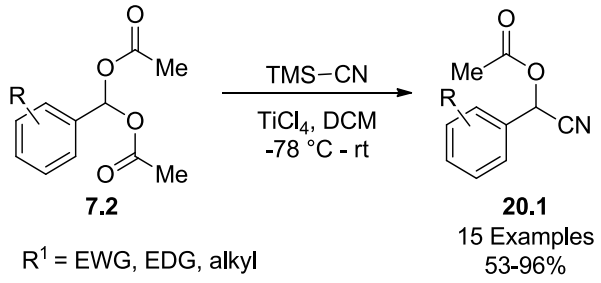
Scheme 18. Reactivity of acylals with TMS-N_3[44]

The reaction is believed to proceed *via* a stepwise route, involving displacement of one of the acyl groups by nucleophilic attack of azide to afford acetate **19.1**. Evolution of N_2 from **19.1** then generates an unstable nitrene **19.2**, with acyl transfer occurring to afford *O*-acyl oxime **19.3**, that then eliminates acetate to afford the observed nitrile **18.1** (Scheme 19).[44]



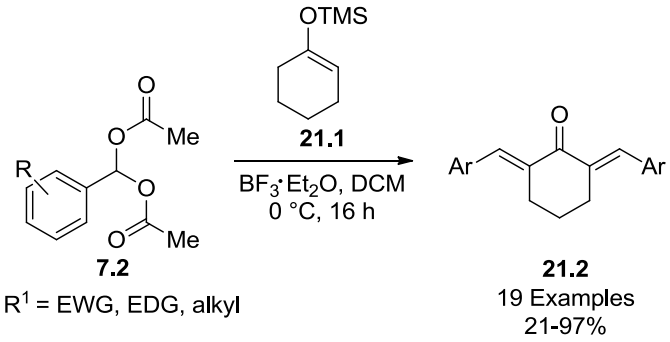
Scheme 19. Mechanism of nitrile synthesis from acylals[44]

Their third contribution explored a similar reaction manifold, investigating the reactivity of acylals towards cyanide reagents.[45] They found that using TMS-cyanide and titanium(IV) chloride as a Lewis acid catalyst gave the best results, synthesizing a range of *O*-acyl cyanohydrins **20.1** in good to excellent yields.[45] The use of TMS-cyanide as a nucleophile in the reaction resulted in mono substitution of one of the acyl groups, allowing the synthesis of cyanohydrin esters **20.1** (Scheme 20).



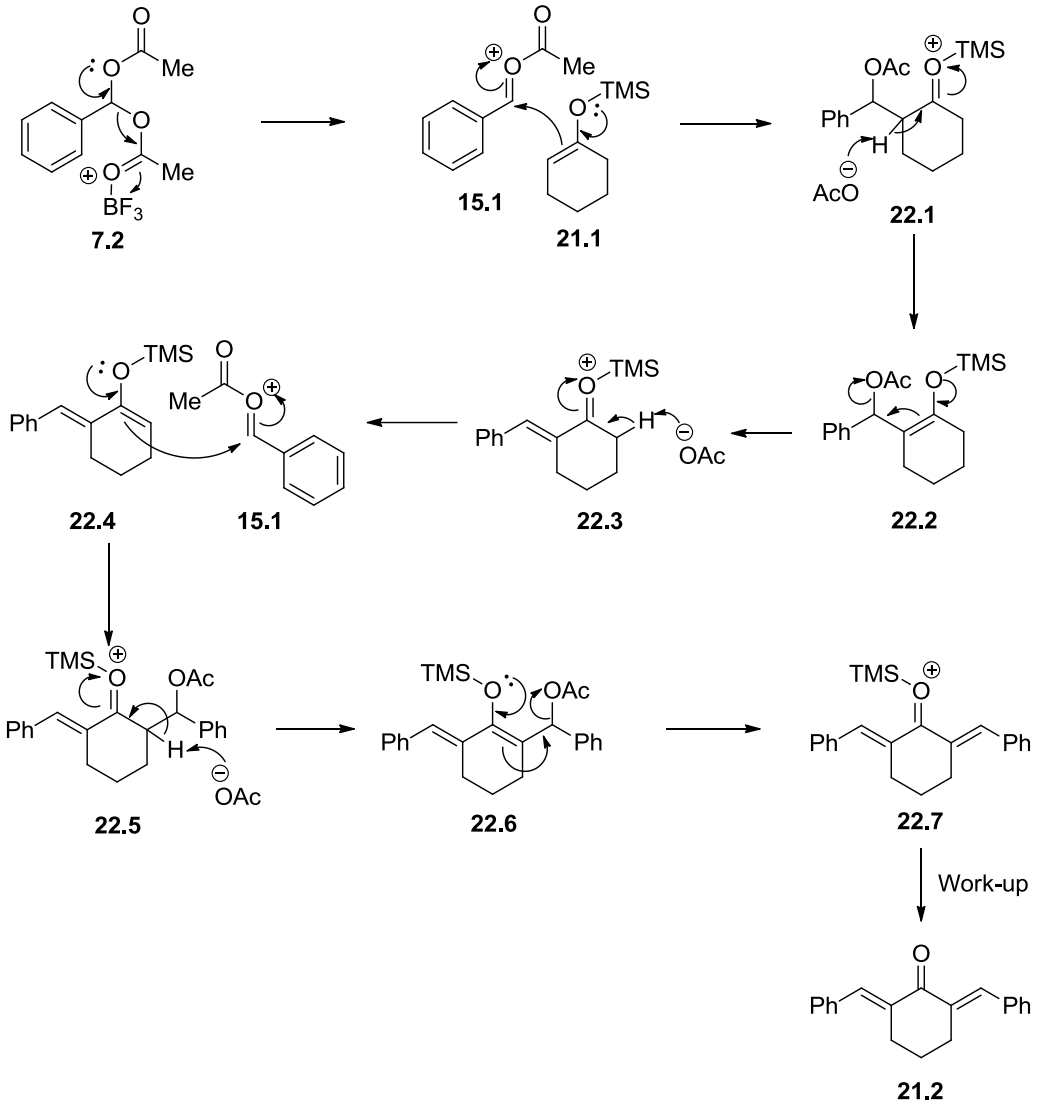
Scheme 20. Synthesis of cyanohydrin esters from acylals[45]

The final report by Sydnes and Sandberg explored the reactivity of acylal **7.2** with silyl enol ethers **21.1**, with boron trifluoride catalyzed reactions leading to the formation of α,α'-bis(arylmethylidene)cylcoalkanones **21.2** in moderate to excellent yields (Scheme 21).[46]



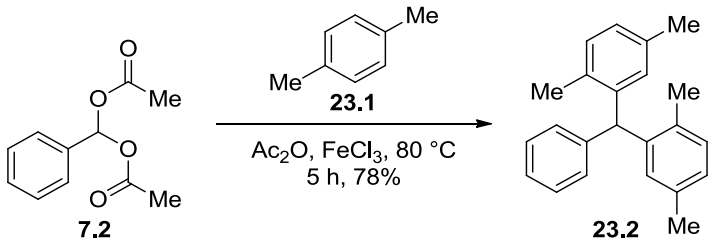
Scheme 21. $BF_3{\cdot}OEt_2$ catalysed reaction of acylals with silyl enol ethers[46]

While no detail of the reaction mechanism was proposed, a reasonable mechanism would involve boron trifluoride catalyzed formation of acyl oxonium **15.1**. Nucleophilic attack of silyl enol ether **21.1** would then afford acetate **22.1**, with an acetate elimination reaction installing the first alkene unit of silyl enol ether **22.4.** Reaction of silyl enol ether **22.4** with a second equivalent of acyl oxonium **15.1** would afford acetate **22.5**, that could then undergo elimination of a second acetate anion equivalent to give oxonium **22.7**, which would lose its silyl ether group to afford the observed bis-α,β-unsaturated ketone **21.2** (Scheme 22).



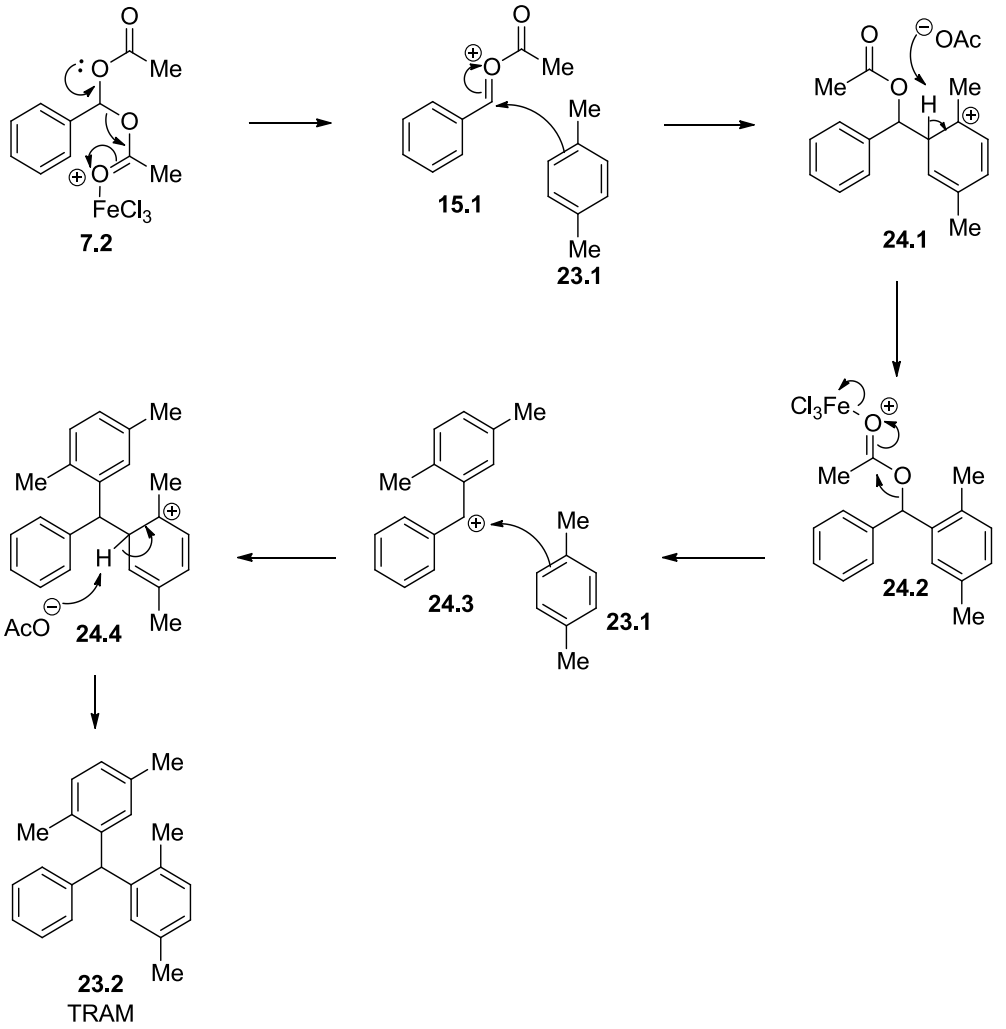
Scheme 22. Proposed mechanism for the synthesis of bis(arylmethylidene)cycloalkanones

Acylals have also found application for the synthesis of triarylmethanes (TRAMs) **23.2**, which are important targets in a number of fields, including materials chemistry, medicinal applications and for the synthesis of dyes.[47] Reaction of acylal **7.2** with *para*-xylene in the presence of an iron catalyst and acetic anhydride led to the formation of TRAM **23.2**. The reaction was shown to proceed using aldehydes instead of acylals, but the acylal is thought to be formed as a more reactive intermediate *in situ* (Scheme 23).[47]



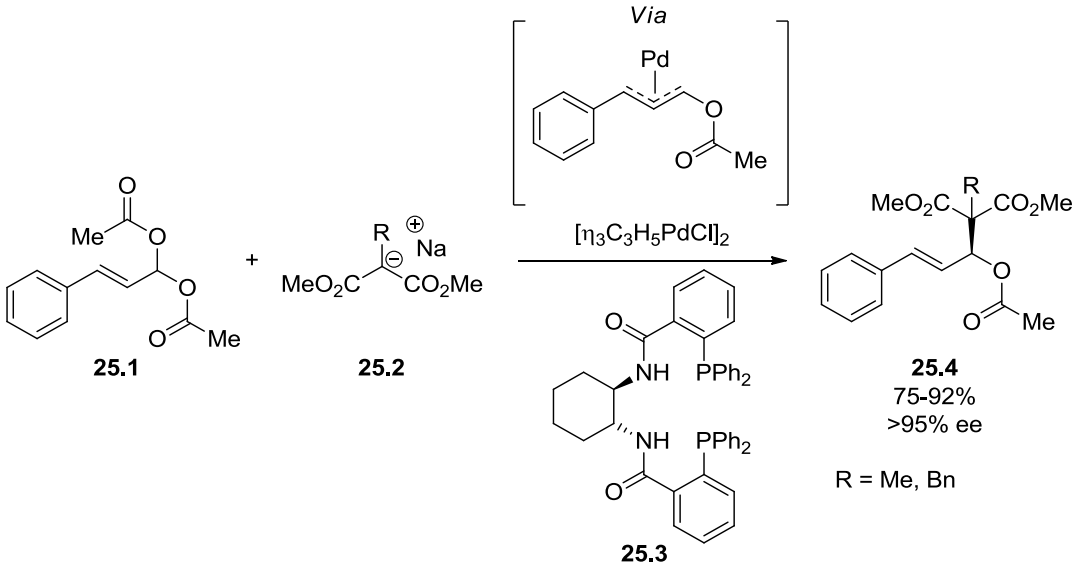
Scheme 23. Reaction of acylals with *p*-xylene to afford triarylmethanes[47]

No mechanism for the formation of triarylmethane **23.2** was proposed in the paper, however, a potential mechanism is suggested in Scheme 24. An iron catalyzed acetate elimination would afford acyl oxonium **15.1**. This intermediate would then undergo electrophilic aromatic substitution of *p*-xylene **23.1** to give acetate **24.1**, with aromaticity being regenerated through deprotonation of **24.1** to give bisarylmethylacetate **24.2**. Acetate elimination via an S_N1 type mechanism would then lead to the generation of stabilized carbocation **24.3**, with a second electrophilic aromatic substitution reaction, and subsequent deprotonation event, affording triarylmethane **23.2** (Scheme 24).



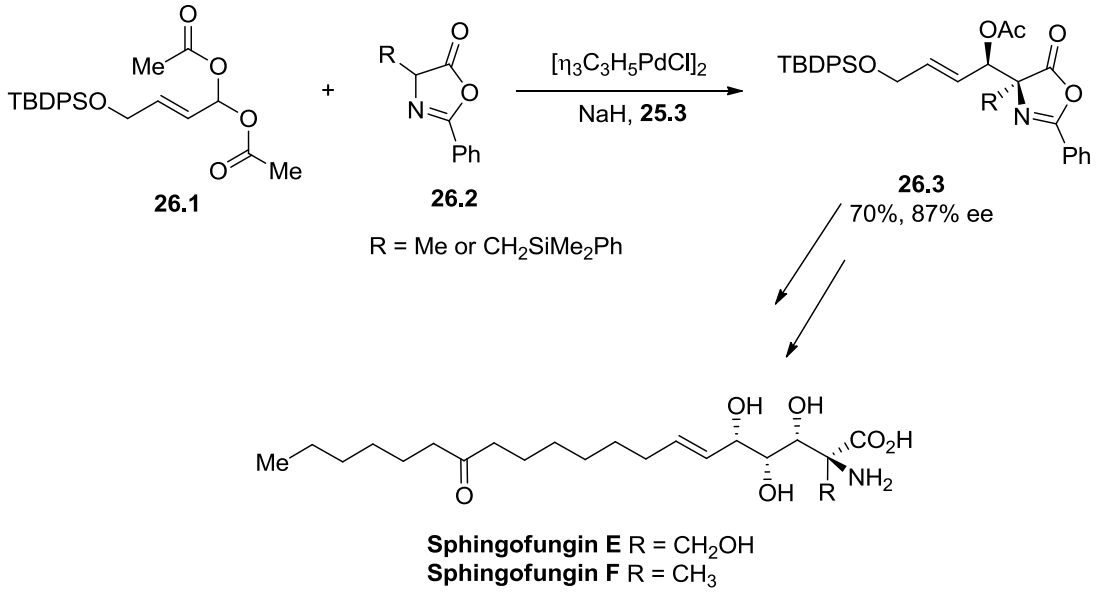
Scheme 24. Proposed mechanism for the formation of TRAMs

Allyl acylals have proven to be one of the most utilized class of reagent, with this area of research being first developed by Trost and coworkers, who published a series of reports on the asymmetric alkylation reactions of allylic acylals, and application of this methodology for natural product synthesis.[48-53] Their initial report described the reaction of allyl diacetate **25.1** with sodium malonate **25.2** to give the monoalkylated product **25.4** in 92% yield and 95% ee, utilizing a palladium catalyst and the chiral bis-phosphine ligand **25.3** (Scheme 25). This alkylation reaction proceeds through formation of a Pd-π-allyl complex which allows for stereoselective nucleophillic attack of the malonate nucleophile **25.2**. The reaction was subsequently optimized to accommodate a wide range of allyl acylals and stabilised carbon nucleophiles, affording the corresponding monoalkylation products in good yield and excellent enantiomeric excess.[51, 52]



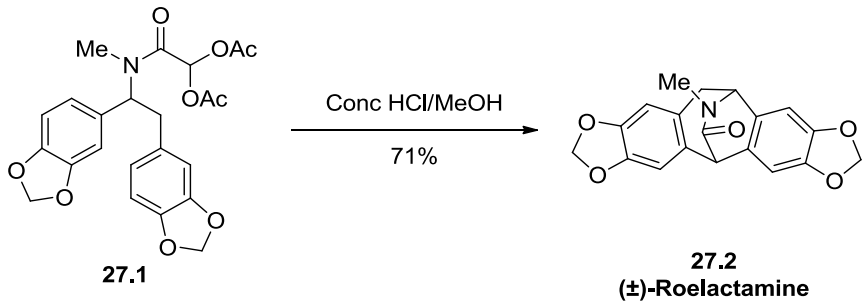
Scheme 25. Asymmetric alkylation reaction of allylic acylal[49]

Trost *et al.* subsequently applied this methodology to the synthesis of the natural products sphingofungins E and F.[50, 53] Both natural products were synthesised from the common intermediate allyl acetate **26.1**, which was synthesised from *O*-silyl protected allyl diacetate **26.1** and oxazolone **26.2** in 70% yield and 87% ee. Allyl acetate **26.3** was used as an advanced intermediate for the synthesis of the natural products sphingofungins E and F in 5.1% (17 steps) and 17% (15 steps) overall yields respectively (Scheme 26).[50, 53]



Scheme 26. Synthesis of sphingofungins E and F utilizing allylic acylal **26.1** as a carbonyl surrogate[50, 53]

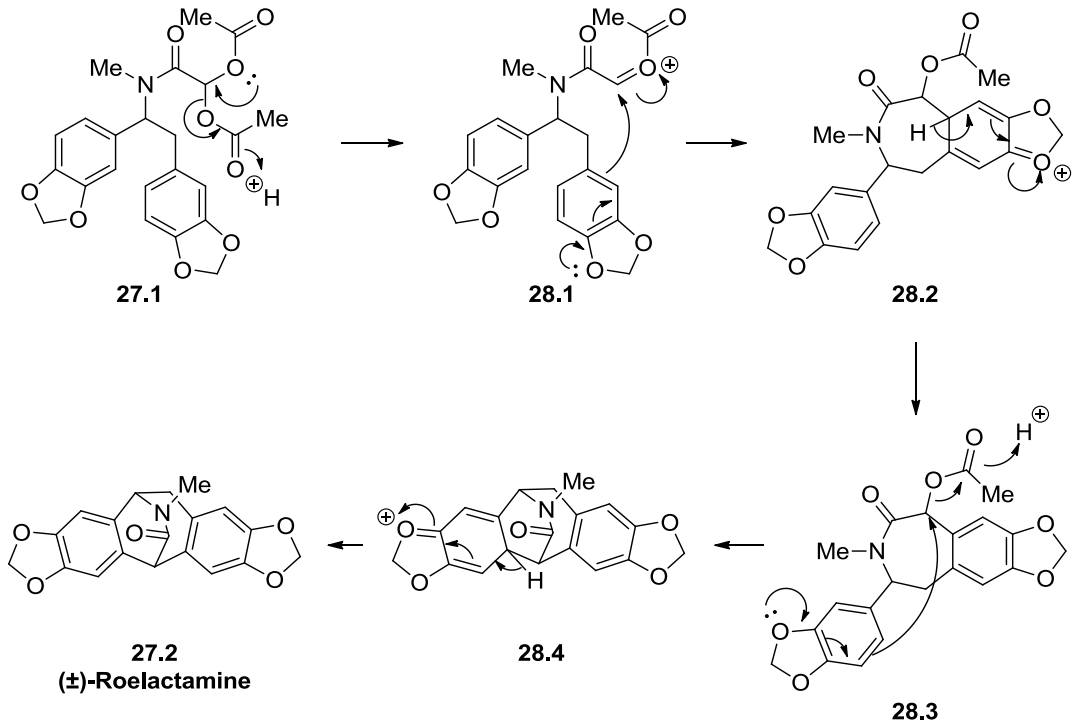
Acylals have also been applied as a substrate for a number of other natural product syntheses, including for the synthesis of roelactamine **27.2** by the Martin group in 2007. The acylal containing tertiary amide **27.1** was treated with concentrated methanolic hydrochloric acid, resulting in a facile double cyclization reaction to give roelactamine **27.2** in 71% yield (Scheme 27).[54]



Scheme 27. Synthesis of roelactamine[54]

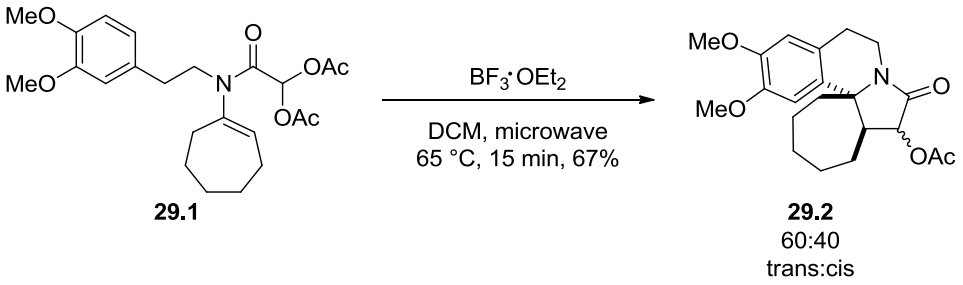
The reaction is proposed to proceed *via* acid catalysed formation of acyl oxonium **28.1**. An intramolecular electrophilic aromatic substitution reaction affords acetate **28.2** which upon deprotonation by acetate gives bicycle **28.3**. A second acid catalysed intramolecular S_N1-like

electrophilic aromatic substitution reaction then affords **28.4**, which after further deprotonation event gives the desired roelactamine product in a 71% yield (Scheme 28).



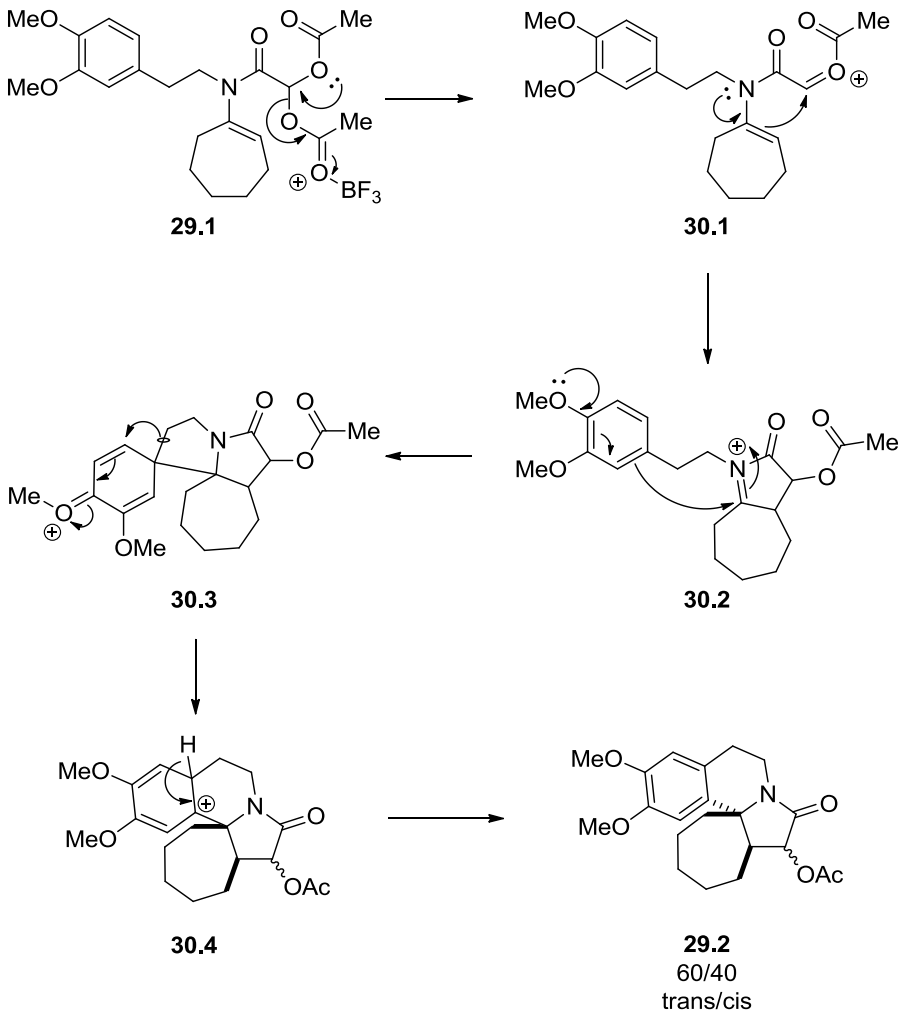
Scheme 28. Proposed mechanism for the synthesis of roelactamine

A second tandem intramolecular acylal cyclisation (IAC) strategy was developed by the Hilton group directed towards the synthesis of erythrina alkaloid derivatives.[55] They first developed the synthesis of a range of key cyclisation precursors **29.1** (one example shown for clarity), which were subjected to a mild BF_3 catalysed cyclisation reaction to give the fused tricycle **29.2** (Scheme 29).



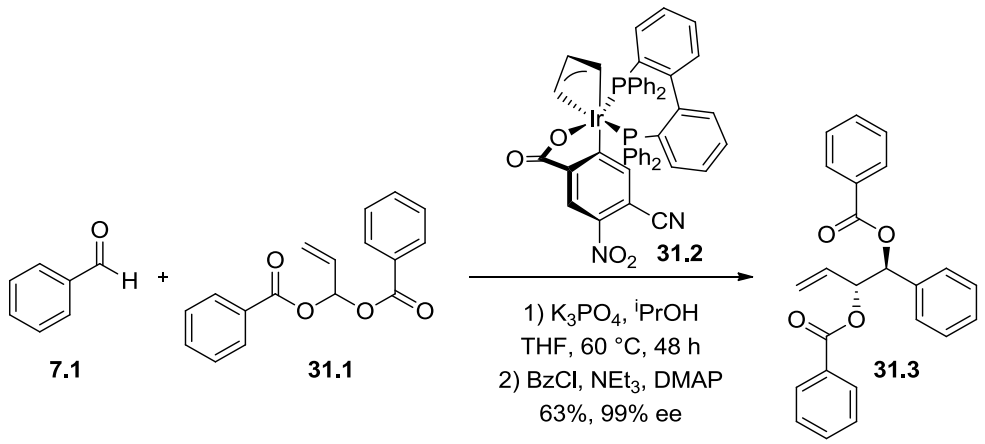
Scheme 29. Intramolecular acylal cyclisation reaction for the synthesis of erythrina alkaloid derivatives[55]

The reaction is believed to proceed *via* intramolecular nucleophilic addition of an enamine fragment at an acyl oxonium species **30.1** to afford *N*-acyl-iminium species **30.2**. An intramolecular electrophilic aromatic substitution reaction then occurs to afford tricycle **30.3**, with an alkyl migration reaction leading to ring expansion to generate carbocation **30.4**. Subsequent, deprotonation then generates the observed tetracyclic product **29.2** in a 60:40 *trans* to *cis* ratio (Scheme 30).



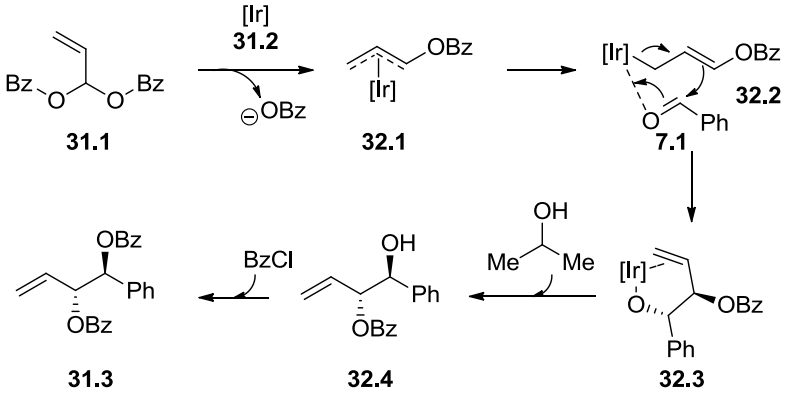
Scheme 30. Proposed mechanism for the synthesis of fused tetracycle **29.2**[55]

Allyl acylal substrates have also been utilised by the Krische group for stereoselective iridium catalysed alkoxyallylation reactions,[56] with allyl *gem*-benzoate **31.1** affording the highest yields and best diastereoselectivities when compared to other acylal substrates. For example, benzaldehyde **7.1** reacted with diacyl **31.1** in the presence of the chiral iridium catalyst **31.2** to afford the anti-alkoxyallylation product **31.3** in 63% yield and an impressive 99% ee, with a dr ratio of 18:1 (Scheme 31).[56] The reaction proceeds under iridium catalysed transfer hydrogenation conditions with isopropanol as the terminal reductant, which facilitates the reductive coupling of the *gem*-dibenzoate **31.1** and benzaldehyde **7.1**.



Scheme 31. Use of vinyl acylal as allyl donors in an iridium catalysed *anti*-alkoxyallylation reactions[56]

The reaction is believed to proceed through formation of Ir-π-allyl complex **32.1**. The iridium migrates to form σ-allyl complex **32.2** (primarily (*E*)), which then reacts with bezaldehyde **7.1** *via* a Zimmerman-Traxler type transistion state to afford *anti*-diastereomer **32.3**. Isopropanol then displaces monobenzoyl diol **32.4** from the iridium catalyst, which was subsequently reacted with benzoyl chloride to give the desired *anti*-bis-benzoyl diol product **31.3** (Scheme 32).



Scheme 32. Proposed mechanism for iridium catalysed *anti*-alkoxylation reaction of vinyl acylals[56]

As described, phenylmethylene diacetate **7.2** and acylals are versatile synthetic reagents that have been applied as substrates in a range of synthetic methodologies. However, remarkably and to the best of our knowledge, phenylmethylene diacetate **7.2** had never been applied as a simple acylating reagent for nitrogen and oxygen nucleophiles. Consequentially, we

now report an investigation into the application of acylals as new, bench stable, acylating reagents for the *N*-/*O*- acylation of primary and secondary amines and alcohols.

1.5 Acylals as Reagents for the *N*-Acetylation of Amines

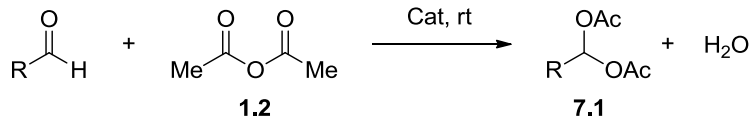
In order to employ acylals as potential new *N*-/*O*- acylating agents it was first necessary to devise a route for their synthesis. The most common methods reported in the literature involve reaction of a parent aldehyde with an anhydride in the presence of a suitable catalyst. The catalysts utilized are primarily based on Brønsted acids,[32, 57-60] Lewis acids,[61-70] as well as the use of iodine,[71] NBS,[72] iron-montmorillonite and zeolites.[73, 74] All these catalytic systems are believed to afford acylals using the same general mechanism described in Scheme 8. The conditions that were chosen for the synthesis of acylal **7.2** were those of Manjula *et al.*[32] utilizing *p*-TSA as a Brønsted acid catalyst. These conditions were reported to afford acylal **7.2** in excellent yield at rt (Scheme 7). Importantly, no arduous purification steps were required, with high purity product obtained after an aqueous sodium carbonate wash, meaning that acylals could potentially be accessed in large quantities.

The choice of parent aldehyde used for the synthesis of the desired acylal was an important consideration. Cost of reagents, ease of synthesis and ease of byproduct removal were some of the factors that were considered. It was decided that either an aromatic aldehyde, or a short chain alkyl aldehyde would best suit our purposes, with benzaldehyde and propionaldehyde identified as potential precursors. Acylal synthesis using benzaldehyde proceeded smoothly to give high purity acylal **7.2** in good yield after 1 h (Table 1 entry 1). However, when propionaldehyde was used as the aldehyde core a number of problems became apparent. Under a range of synthetic conditions the resultant acylal proved to be much less stable and more temperamental than the benzaldehyde derivative, readily decomposing to afford undesired side products, believed to be formed through unwanted elimination or aldol side reactions.

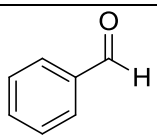
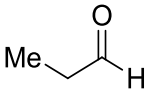
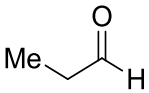
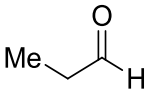
Therefore, while the use of propionaldehyde resulted in 100% conversion, the yield of the desired acylal was significantly reduced to 45% (Table 1 entry 2). In an attempt to alleviate this issue, alternative conditions were explored using $Cu(BF_4)_2{\cdot}xH_2O$ as a Lewis acid catalyst (at 1 mol%).[70] Although the crude yield of the desired acylal was greatly improved, the presence of multiple minor impurities meant that the acylation reagent required further purification by column chromatography that resulted in a significant loss in yield. This was undesirable, and

essentially rendered the use of propionaldehyde as the aldehyde core unviable. Consequently benzaldehyde was chosen as the core aldehyde for acylal synthesis (Table 1).

Table 1. Synthesis of acylals



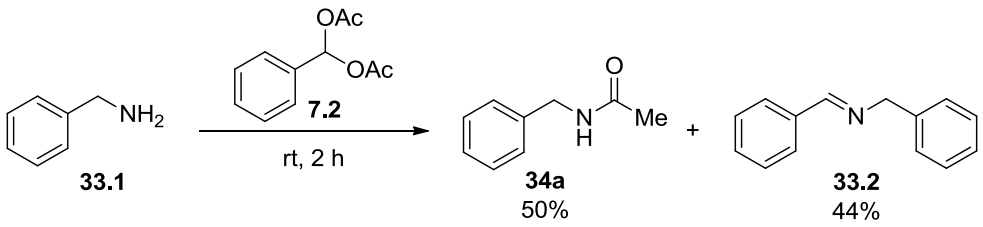
R = Alkyl, Aryl

Entry	Aldehyde	Catalyst	Reaction Time	Aldehyde Conversion (%)	Selectivity Towards Acylal (%)
1		*p*-TSA	1 h	100	95
2		*p*-TSA	1 h	100	45
3		$Cu(BF_4)_2 \cdot xH_2O$	5 min	100	65
4		$Cu(BF_4)_2 \cdot xH_2O$	1 min	100	68

Reaction conditions: Entries 1 and 2, aldehyde (1 equiv.), acetic anhydride (2 equiv.), cat (0.1 equiv.). Entries 3 and 4, aldehyde (1 equiv.), acetic anhydride (1.5 equiv.), cat (0.01 equiv.).

Acetylation of benzylamine **33.1** using phenylmethylene diacetate **7.2** was the first *N*-acylation reaction to be investigated. A range of conditions were screened, encompassing solvent, reaction time, reaction temperature and number of equivalents of acylating agent (Table 2). As shown in Table 2 the choice of solvent had little effect on the distribution of products, with the reaction also found to perform well under solvent free conditions (entry 4). However, as shown for entries 1-4, although there was good conversion of benzylamine at rt, selectivity for formation of acetamide **34a** was poor at around 50%. Unsurprisingly, the major

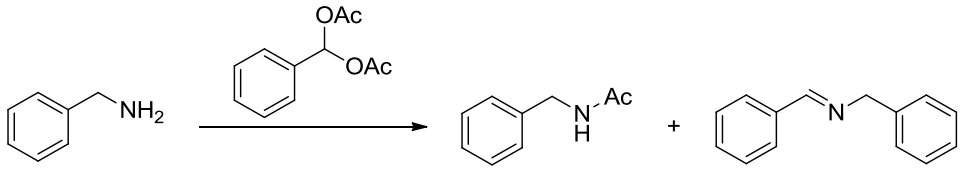
side product formed was due to reaction of benzylamine with benzaldehyde (produced as a byproduct of the acetylation reaction) to form imine **33.2** (Scheme 33).



Scheme 33. Competing side reaction during acetylation of benzylamine

Imine formation is a reversible process, whereas acetamide formation is irreversible. Therefore, it was proposed that the equilibrium for imine formation could be perturbed towards acetamide formation under more forcing conditions. To achieve this aim, a number of routes were explored. Firstly, the reaction time was extended to 16 h and the amount of acylal **7.2** employed increased from 1.5 to 5 equivalents, however, this had little or no effect on the ratio of amide to imine formed (entries 4-7). Reaction temperature was the next variable to be changed, with increased reaction temperature, leading to greater quantities of acetamide being produced, with the best results achieved at 70 °C. The optimal conditions were found to be 1.5 equivalents of acylating agent **7.2** at 70 °C for 16 h solvent free. The crude amide product could be purified directly *via* column chromatography, without the need for any aqueous work up.

Table 2. Optimization of *N*-acetylation reactions of benzylamine

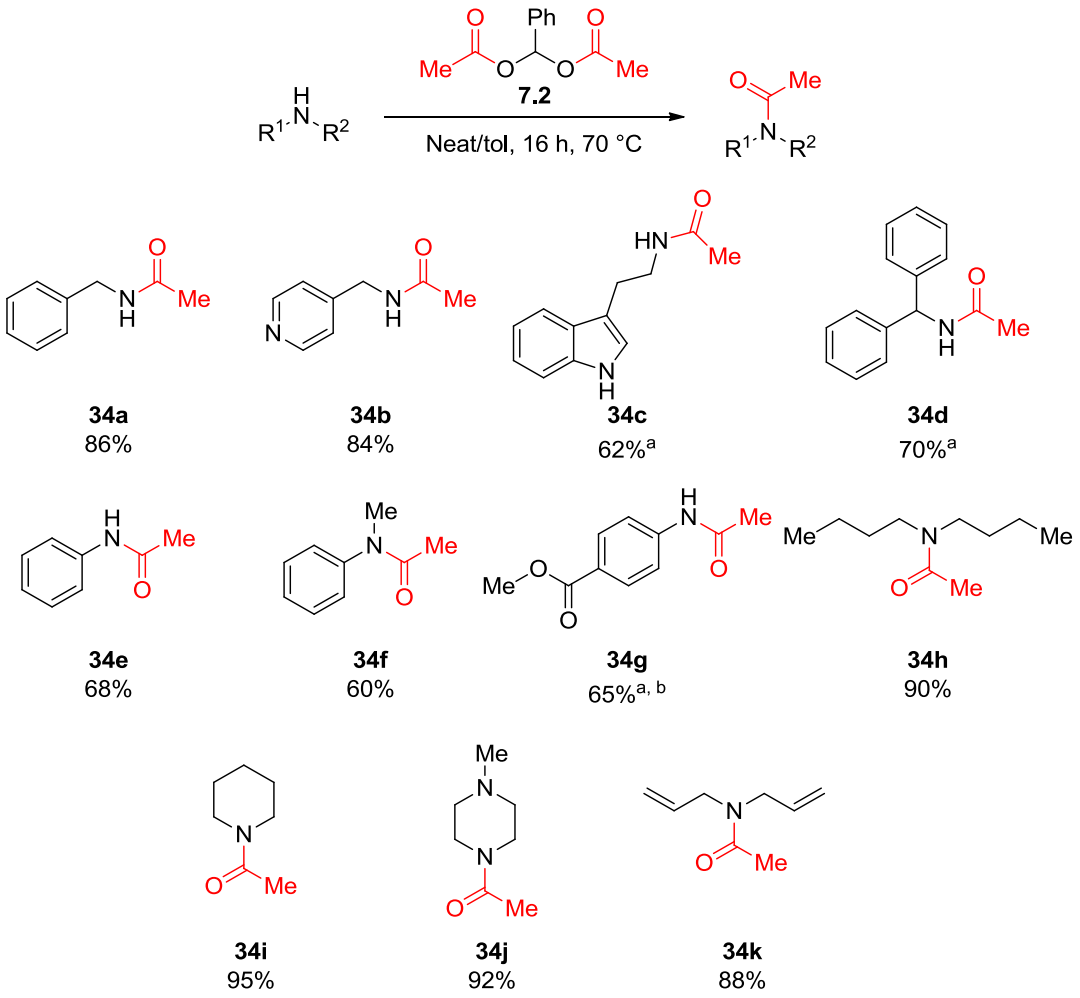


Entry	Solvent	Equiv. *gem*-Diacetate	Reaction time (h)	Temperature (°C)	Amine Conversion (%)	Acetamide: Imine
1	EtOAc	1.5	2	rt	95	50:50
2	Tol	1.5	2	rt	90	48:52
3	DCM	1.5	2	rt	92	51:49
4	-	1.5	2	rt	94	53:47
5	-	1.5	16	rt	99	54:46
6	-	2	16	rt	98	55:45
7	-	5	16	rt	99	52:49
8	-	1.5	16	50	99	65:35
9	-	1.5	16	60	99	70:30
10	-	1.5	16	70	99	95:5

With these optimized conditions in hand a range of amines were screened for reaction with phenylmethylene diacetate **7.2** affording a range of eleven acetamides **34a-k** (Reaction conditions; 1 mmol of amine, 1.5 equiv. **7.2**, 12 h, 70 °C. [a]toluene required as solvent. [b]24 h reaction time.

Scheme 34). *N*-acetylation of both primary, secondary and cyclic amines proceeded with good conversion to afford their corresponding acetamides in 60-95% isolated yield. It is worth noting that typtamine was cleanly *N*-acetylated to afford **34c** in 62% yield, with no acetylation of the indole nitrogen being observed. Pleasingly, even sterically hindered branched amines gave their corresponding acetamides **34d** in 70% yield. Less reactive primary and secondary anilines were also efficiently *N*-acetylated, albeit with slightly reduced isolated yields 60-68%

(**34e** and **34f**), including the electron deficient amide **34g** which was formed in a 65% yield. For amines that proved to be insoluble in acylal **7.2**, then toluene was used as a co-solvent to ensure a homogeneous reaction mixture.

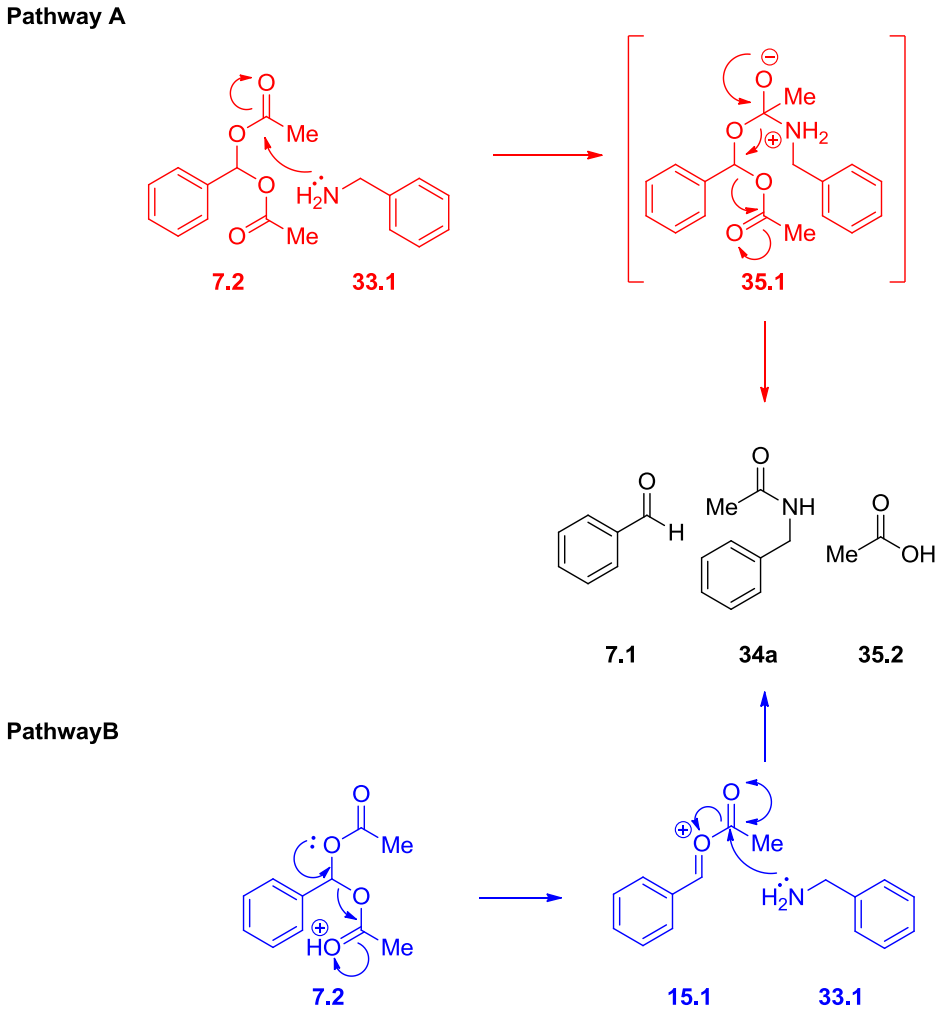


Reaction conditions; 1 mmol of amine, 1.5 equiv. **7.2**, 12 h, 70 °C. [a]toluene required as solvent. [b]24 h reaction time.

Scheme 34. Scope of *N*-acetylation reactions of amines with acylal **7.2**

It was proposed that the mechanism of acetamide formation could potentially proceed *via* one of two potential pathways. Pathway A would proceed *via* nucleophilic attack of amine **33.1** into one of the carbonyl bonds of the acetate groups of acylal **7.2** to give tetrahedral carbinolamine intermediate **35.1**. Reformation of the carbonyl bond would then lead to formation of acetamide **34a** as well as formation of one equivalent of benzaldehyde **7.1** and

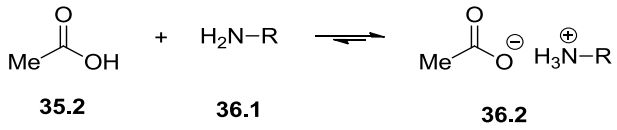
acetic acid **35.2**. Pathway B would proceed through acetate elimination to give acyl oxonium **15.1**, followed by nucleophilic attack of the amine **33.1** at the acyl carbonyl bond to afford the observed acetamide **34a**, once again resulting in one equivalent of benzaldehyde **7.1** and acetic acid **35.2** as by-products (Scheme 35).



Scheme 35. Potential mechanisms for the formation of acetamide **34a**

In order to investigate which pathway was operating a series of experiments were conducted. In both of the proposed reaction pathways, for every equivalent of acetamide produced, then an equivalent of acetic acid would also be produced. It would be expected that every equivalent of acetic acid produced would react with unreacted amine to form an acetate salt, preventing it acting as a nucleophile in the reaction. If this were to happen then the maximum conversion would be expected to be only 50% however, complete conversion was

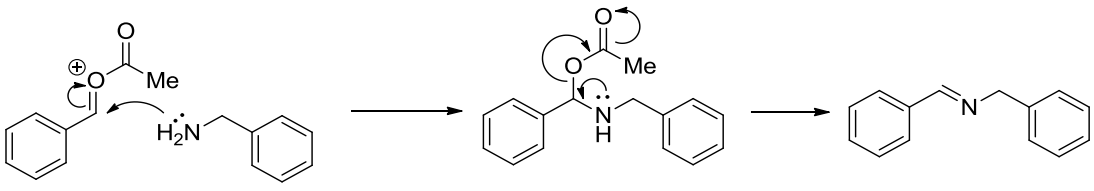
clearly being observed at elevated temperatures. When the pH of the reaction was monitored overtime the reaction remained neutral (pH 7) throughout the course of the reaction, until the end of the reaction when it became acidic in nature. This would suggest that the reaction is self-buffering. Therefore, it is proposed that the amine acetate salt is indeed being formed *in situ*, but is being formed reversibly allowing for free amine to be continuously generated, in the reaction that can then irreversibly react with excess acylal to afford the observed acetamide (Scheme 36).



35.2 **36.1** **36.2**

Scheme 36. Self-buffering pH control mechanism operating in acetylation reaction

It is also important to consider the formation of imine by-product. For pathway A it is proposed that the imine would be formed by acid catalysed reaction of unreacted amine and the benzaldehyde produced. However, for pathway B the imine could also be formed through nucleophilic attack of amine at the oxonium carbonyl of intermediate **15.1** to give *O*-acyl-hemi-carbinolamine **37.1** (Scheme 37). In order to try and investigate which method of imine formation was occurring, the reaction was performed under basic conditions, since conventional imine formation from reaction of an amine and an aldehyde, does not generally occur under basic conditions. 2 equiv. of K_2CO_3 was added to the reaction to maintain a basic pH throughout the course of the reaction. It was found that imine **33.2** was indeed formed under these basic conditions, suggesting that the reaction proceeds *via* pathway B. It is important to note that under basic conditions the reaction did not reach 100% conversion, with the reaction stalling at 50% acetamide and 50% imine, which is due to the stability of imines under basic conditions.



15.1 **33.1** **37.1** **33.2**

Scheme 37. Pathway B for imine formation

The acetylation reaction of benzylamine **34.1** with acylal **7.2** was followed by ^{1}H NMR spectroscopic analysis at 70 °C (in toluene-d8), with the data summarised in Figure 3. As can be seen, consumption of the amine occurs within the first 30 minutes (Figure 3). However, imine formation occurs slightly faster than acetamide formation reaching 34% after 30 minutes. Slowly, over time reversible imine formation regenerates the amine, which reacts with oxonium species **15.1** to irreversibly afford acetamide **34a** as witnessed by the gradual increase in acetamide and decrease in imine (Figure 3).

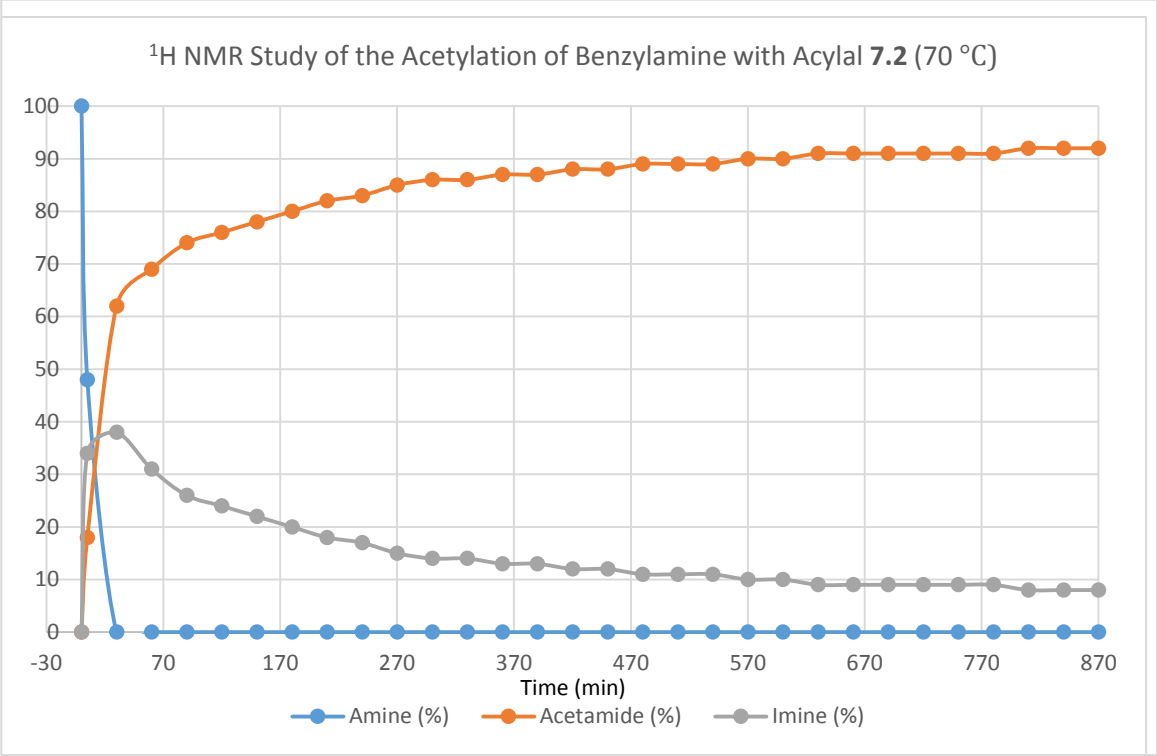
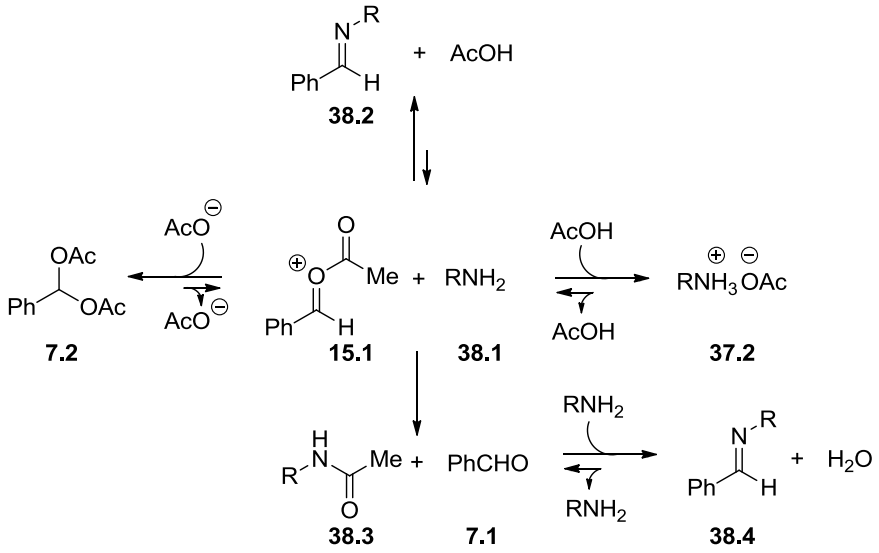


Figure 3. A timeline graph to show acetamide and imine formation during the course of acetylation reaction using acylal **7.2**.

With all this information in hand, a possible overall mechanism for the *N*-acetylation of amines by acylal **7.2** is presented below (Scheme 38). Acid catalysed formation of acyl oxonium **15.1** from acylal **7.2** is coupled with a loss of acetic acid. Nucleophilic attack of amine **38.1** (which is in equilibrium with its acetate salt **37.2**) into the oxonium carbonyl of acyl oxonium **15.1** would lead to the reversible formation of imine **38.2**. Alternatively nucleophilic attack of amine **38.1** can occur at the acyl carbonyl of acyl oxonium **15.1** to irreversibly afford acetamide **38.3** and

one equivalent of benzaldehyde **7.1**. Benzaldehyde **7.1** is able to further react with one equivalent of amine **38.1** to reversibly generate imine **38.2**. Both routes that lead to the formation of imine **38.2** are reversible, so this allows for the irreversible formation of acetamide **38.3** that act as a thermodynamic sink, to perturb all the equilibria allowing for total conversion of amine **38.1** to acetamide **38.3** (Scheme 38).

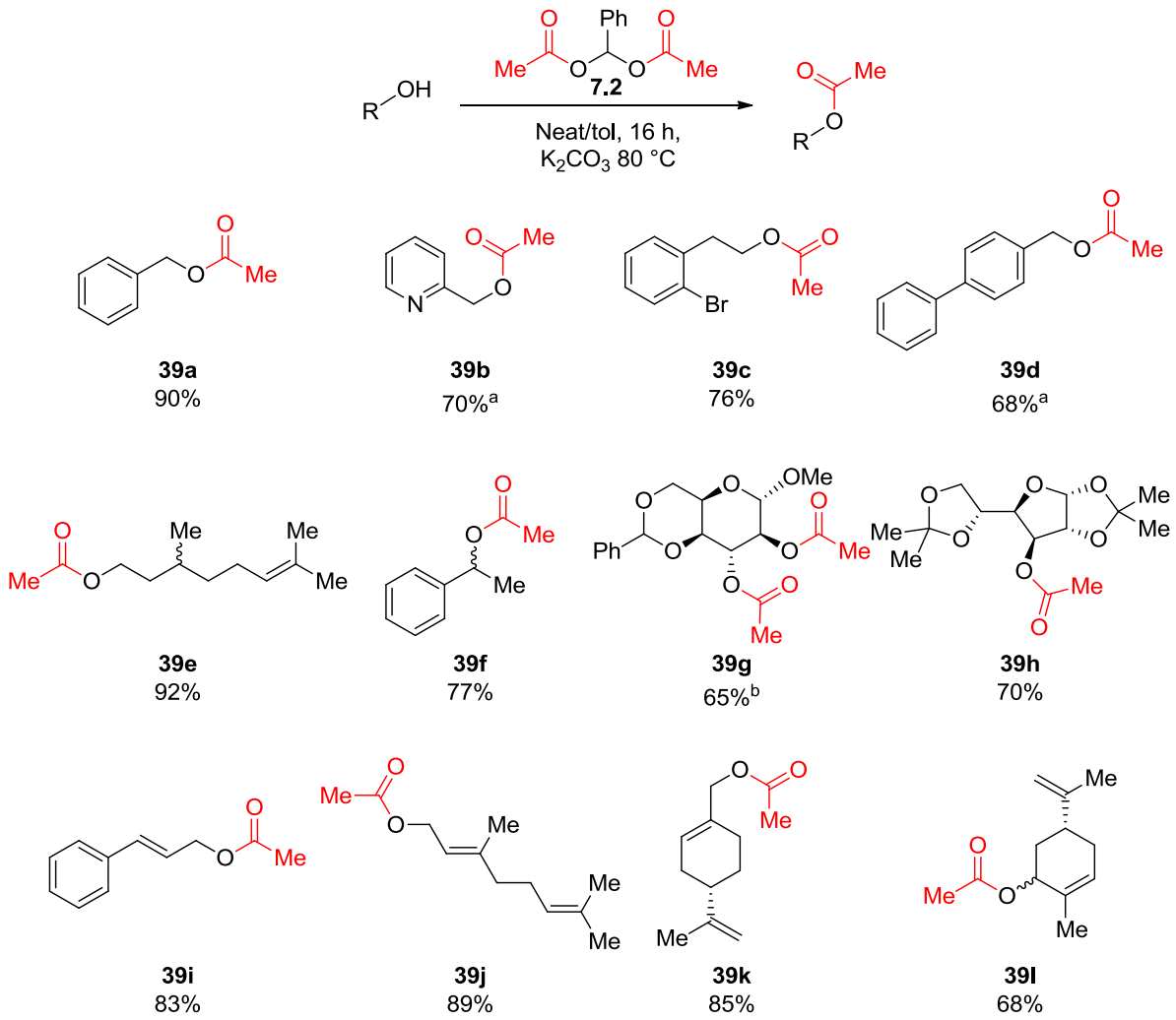


Scheme 38. Overall mechanism for the *N*-acetylation of amines by acylal **7.2**

1.51 Acylals for the *O*-Acetylation of Alcohols

O-acylation reactions of alcohols are also an important synthetic tool, either through thier use as a reversible protecting group strategy for alcohols, or for the synthesis of ester products.[2, 75] Consequently, it was decided to explore whether acylal **7.2** could also be used for the *O*-acetylation of alcohols. The neutral solvent free conditions that were applied for the *N*-acylation of amines were unsuccessful for the *O*-acylation of less nucleophilic alcohols. In the absence of the self-buffering nature of the amine (Scheme 36) the acetic acid formed as a by-product appeared to retard the *O*-acetylation reaction and degrade acylal **7.2**. However, it was found that the inclusion of an inorganic base resulted in clean *O*-acylation of the alcohol, which functions to neutralize the acetic acid as it is produced, as well as deprotonating the alcohol to increase its nucleophilicity.

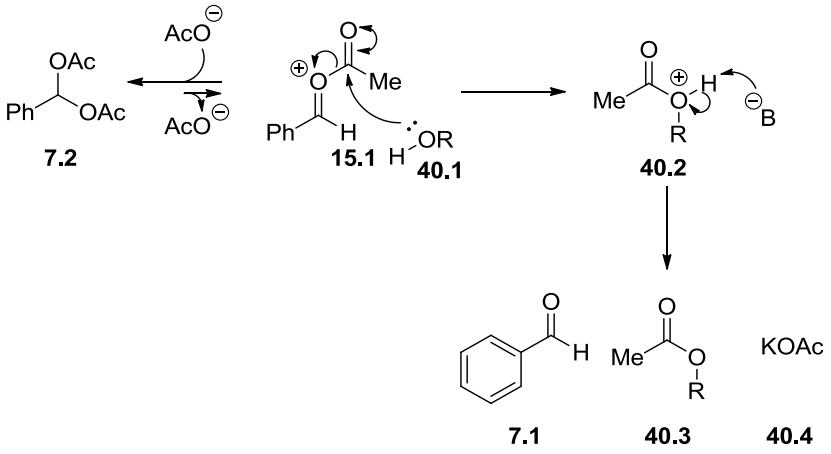
After a brief optimization study, optimal conditions were found to be an elevated reaction temperature to 80 °C, and inclusion of two equivalents of potassium carbonate (K_2CO_3), using 1.5 equivalents of acylal **7.2**. These optimized conditions were applied to a range of eleven primary and secondary alcohols which gave the corresponding acetate esters in 68-92% yield (Scheme 39). Alcohol substrates that were successfully *O*-acetylated include; cyclic, acyclic, alkyl, vinyl, heterocyclic alcohols and diols **39a-l**. Although phenols were not acylated under these conditions. Important observations to note include the fact that *O*-acetylation of 2-pyridinemethanol proceeded to give acetate **39b**, with no evidence of products arising from *N*-acetylation of the pyridine nitrogen. The diol fragment of benzylidene-protected glucose derivative underwent bis-acetylation to give diacetate **39g** in 65% yield. Carveol acetate **39l** was formed with no evidence of any competing base catalyzed elimination reaction having occurred to afford diene products. Good yields were obtained for the formation allylic alcohol acetates **39i-l**, which are useful products that are often used as substrates for palladium allyl nucleophilic addition chemistry.



Reaction conditions; 1 mmol of alcohol, 1.5 equiv. **7.2**, 2.0 equiv. K_2CO_3, 16 h, 80 °C. [a]24 h reaction time. [b] 3 equiv. **7.2**

Scheme 39. Scope of *O*-acetylation reactions of alcohols using acylal **7.2**

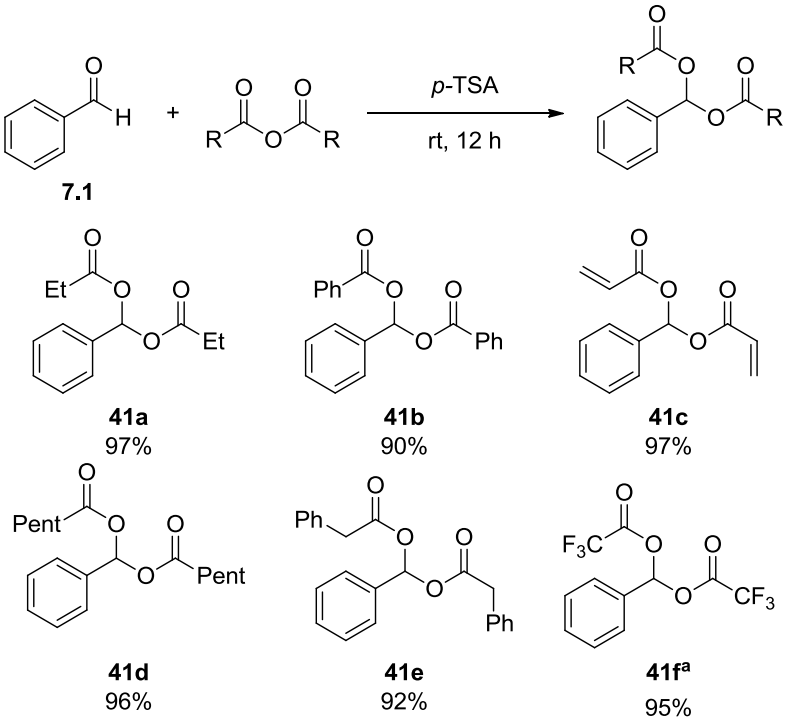
The mechanism of the *O*-acetylation of alcohols using acylal **7.2** is believed to proceed in a much more simplistic manor than that for the *N*-acetylation of amines. Nucleophilic attack of alcohol **40.1** into the acyl carbonyl of acyl oxonium **15.1** will lead to the formation of of protonated ester **40.2**. Deprotonation with K_2CO_3 will lead to formation of ester **40.3**, as well as formation of one equivalent of benzaldehyde **7.1** and potassium acetate **40.4** (Scheme 40).



Scheme 40. Mechanism for the *O*-acetylation of alcohols with acylal **7.2**

1.52 Use of Acylals for the *N-/O*-Acylation of Benzylamine and Benzyl Alcohol

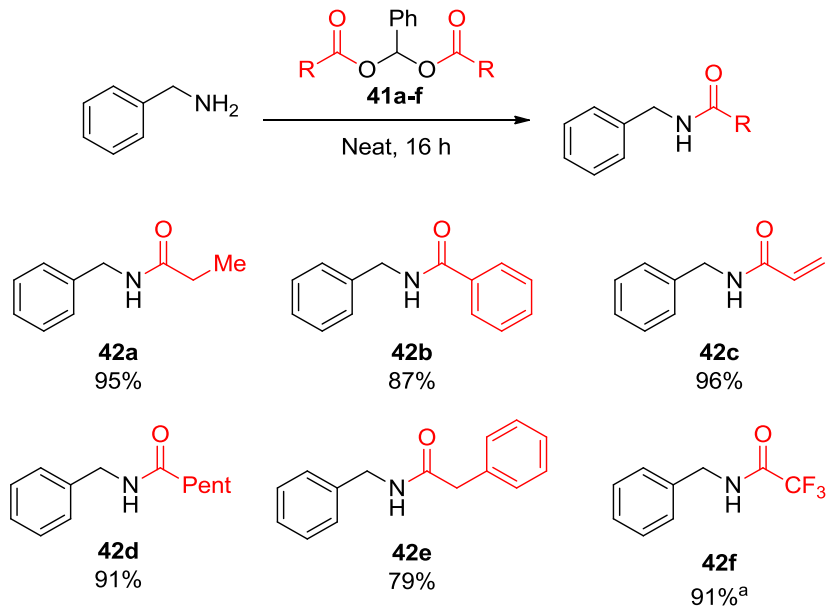
After carrying out successful *N-/O*-acetylation reactions of a range of amines and alcohols, it was decided to broaden the scope of the acylating reagent to determine whether other acyl groups could be transferred in this manner. A range of five acylals **41a-e** containing different acyl donor groups were synthesized using the same methodology developed previously for the synthesis of phenylmethylene diacetate **7.2**. Synthesis of the trifluoroacetyl derivative **41f** required more forcing conditions that employed trifluoroacetic acid as a catalyst, which afforded an acylal product that was used without further purification. Exposure of acylal **41f** to water or atmospheric moisture, led to its rapid decomposition (Scheme 41).



Reaction conditions; 1 equiv. **7.1,** 1.5 equiv. anhydride, 0.1 equiv. *p*-TSA. [a] 1 equiv. **7.1,** 1.5 equiv. anhydride, 0.1 equiv. TFA.

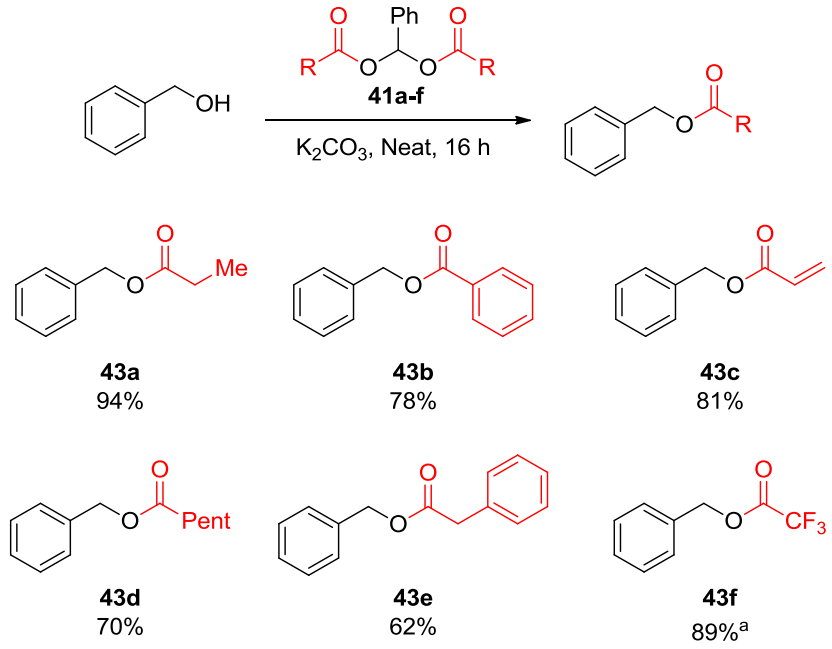
Scheme 41. Synthesis of a range of acylals **40a-f**

These diacyl reagents **41a-f** were then used for a series of representative *N-/O*-acylation reactions of benzylamine and benzyl alcohol respectively. *N*- and *O*-acylation reactions using this range of acylals **41a-f** (including short and long chain alkyl, acryloyl, benzoyl, phenyl acetyl and trifluoroacetyl groups) proved successful without the need for any further optimization affording a range of six benzylamides **42a-f** and six benzyl esters **43a-f** in 79-96% and 62-94% yields respectively (Scheme 42 and Scheme 43).



Reaction conditions; 1 mmol of amine, 1.5 equiv. diacylate, 16 h, 70 °C. [a]1 mmol of amine, 1.5 equiv. diacylate, rt 1 h

Scheme 42. N-acylation reactions of benzylamine using acylals **41a-f**



Reaction conditions; 1 mmol of alcohol, 1.5 equiv. diacylate, 2.0 equiv. K_2CO_3, 16 h, 90 °C. [a]1 mmol of alcohol, 1.5 equiv. diacylate, 2.0 equiv. K_2CO_3, rt 1 h.

Scheme 43. O-acylation reactions of benzyl alcohol using acylals **41a-f**

These type of amide and ester compounds have numerous potential applications. For example, acrylamides **42c** are routinely used as monomers for polymerization chemistry, whilst triflouroacetyl amides are privileged medicinal chemistry motifs, which are often used for the synthesis of highly active drug molecules. Such as Valrubicin which is used for bladder cancer treatment (Figure 4).

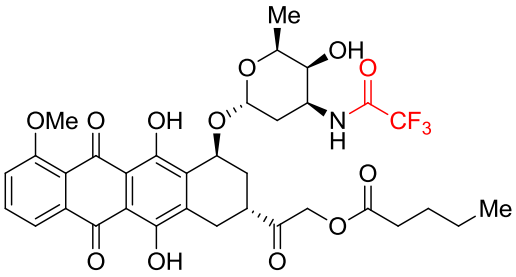
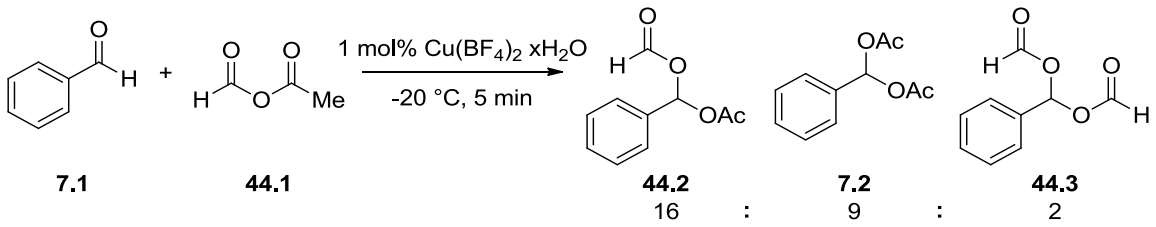


Figure 4. Structure of Valrubicin

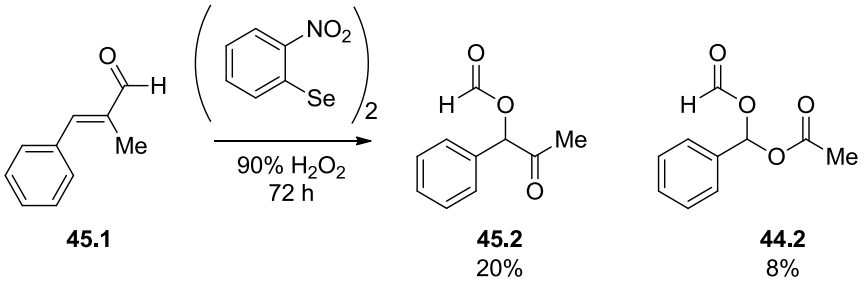
Having demonstrated that acylals could be used for the acylation of amines and alcohols, our attention turned to developing an analogous formylating reagent. *N*-formylation of amines is a highly important reaction in organic synthesis and medicinal chemistry, with formamides used as versatile synthetic intermediates, and often present as fragments in a number of medicinally active compounds.[76-78] For example, formylation chemistry has been heavily utilized in peptide synthesis due to the ease of carrying out late-stage formyl deprotection,[76, 77, 79, 80] while formamides have also found widespread application as precursors for the synthesis of isocyanides and formamidines.[76, 81, 82] With this utility in mind, our efforts next turned towards the synthesis of a formyl version of acylal **7.2**. As well as the methods covered earlier in this report, there a number of techniques for the synthesis of formamides. Including the use of chloral, formic acid, formaldehyde and formates as the formyl source.[83] These are either reacted directly or in conjunction with a range of catalsyst including, mild base (ammonium carbonate), mild acid (pTSA, MTSA), polymer supported acid/base catalyst and metal catalyzed formation.[83]

1.6 *N*-Formylation of Amines

It was decided that a *gem*-diformyl variant was likely to be unviable due to the inherent instability of formic anhydride, and so it was decided to attempt to synthesize a mixed 1,1-formyl acetate **44.2**, reasoning that its more reactive formyl group would be selectively transferred. In order to obtain the desired compound our standard synthesis needed to be altered. An adaptation of the Chakraborti 1,1-diacetate synthesis was utilized (Scheme 44),[70] involving treatment of benzaldehyde **7.2** and *O*-formylacetate **44.1** with a catalytic amount of $Cu(BF_4)_2xH_2O$ at -20 °C. This reaction gave a mixture of products containing (formyloxy)(phenyl)methyl acetate **44.2**, phenylmethylene diacetate **7.2** and *gem*-diformal **44.3** in a 16:9:2 ratio (Scheme 44). These products could be easily separated by chromatography to afford pure (formyloxy)(phenyl)methyl acetate **44.2** in 59% yield and phenylmethylene diacetate **7.2** in 25% yield respectively. Although resonances for *gem*-diformal **44.3** could be seen in ^{1}H NMR spectra of the crude reaction product, is proved to be unstable, as predicted decomposing on exposure to silica. The observed formation of a mixture of products is a consequence of this reaction proceeding *via* an intermolecular pathway.[33, 34] To the best of our knowledge, (formyloxy)(phenyl)methyl acetate **44.2** has only been prepared once previously, where it was isolated as a side product of an oxidation reaction in a meagre 8% yield by Syper *et al.* (Scheme 45).[84]

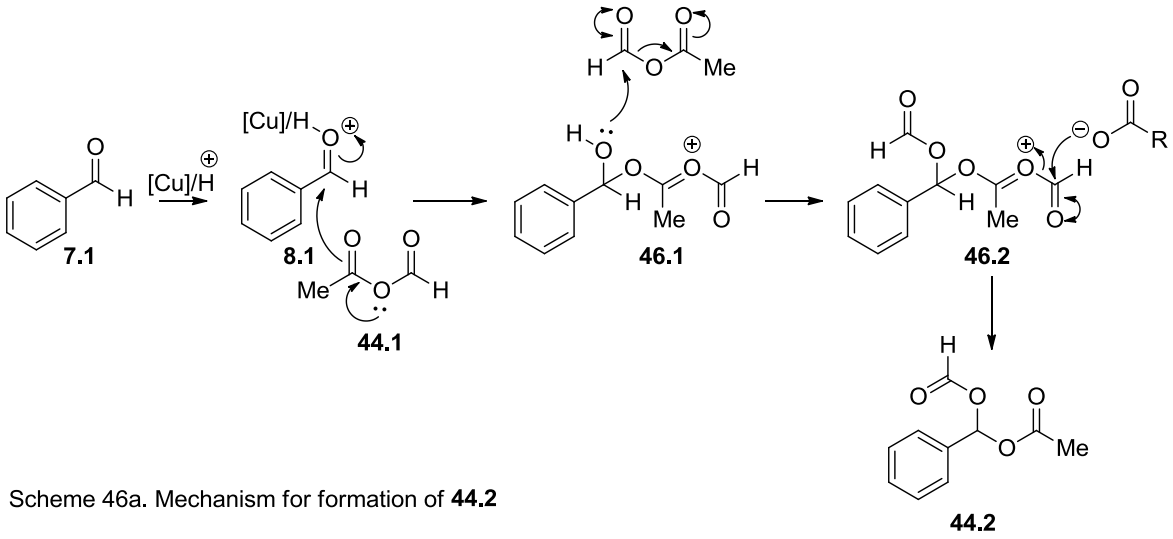


Scheme 44. Synthesis of (formyloxy)(phenyl)methyl acetate.

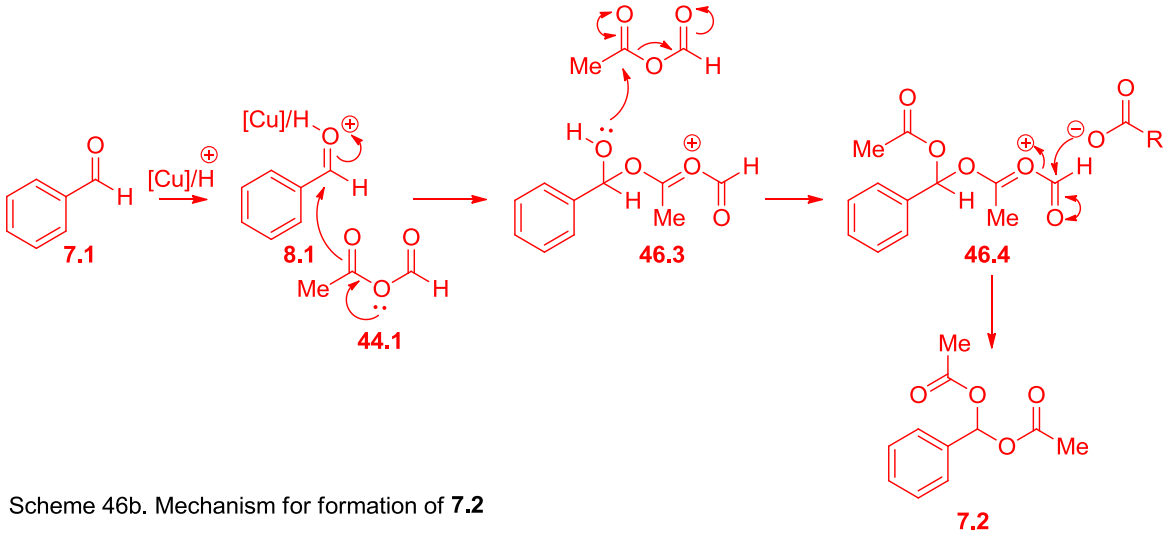


Scheme 45. Synthesis of (formyloxy)(phenyl)methyl acetate **44.2** by Syper[84]

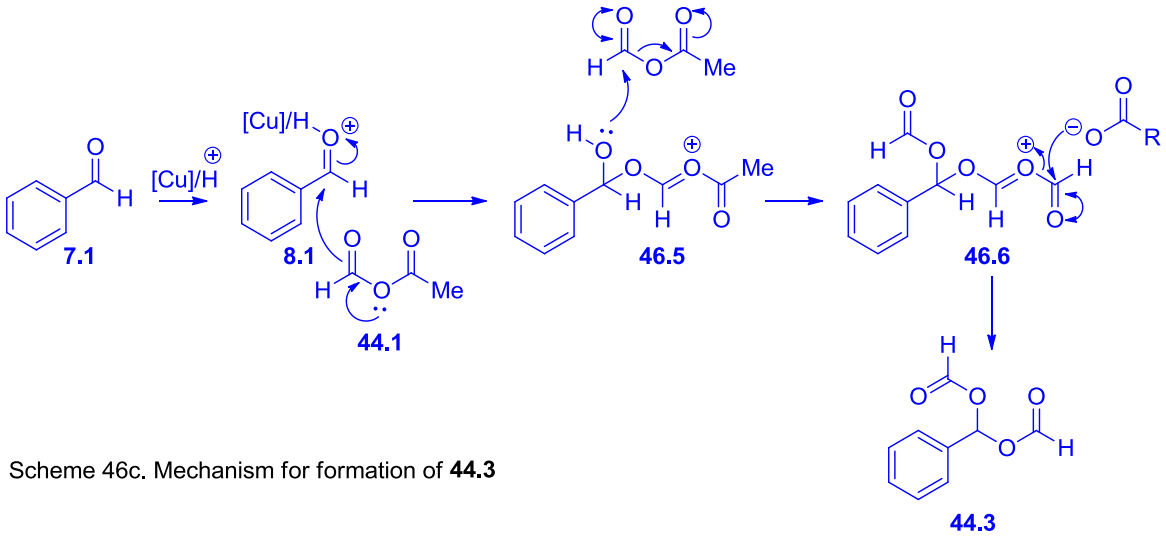
Therefore we decided to investigate the use of (formyloxy)(phenyl)methyl acetate **44.2** for the *N*-formylation of amines. The mechanism for the formation of **44.2** is likely to proceed as described earlier, with attack of mixed anhydride **44.1** into the carbonyl bond of oxonium **8.1** affording acyloxonium **46.1**. The hydroxy group present in acyloxonium **46.1** is able to attack into the formyl fragment of anhydride **44.1** to afford acyl oxonium **46.2**. Anhydride regeneration then affords the observed (formyloxy)(phenyl)methyl acetate **44.2** (Scheme 46a, shown in black). Formation of acylal **7.2** (shown in red) proceeds *via* a similar mechanism, however, attack of the hydroxyl group of **46.1** at anhydride **44.1** occurs at the acyl carbonyl (Scheme 46b). Finally, formation of *gem*-diformal **44.3** (shown in blue) proceeds *via* attack of the formate half of mixed anhydride **44.1** into the carbonyl bond of oxonium **8.1** affording acyloxonium **46.5**. The hydroxy group present in acyloxonium **46.5** then attacks the formate carbonyl of anhydride **44.1** to afford acyl oxonium **46.6**. Anhydride regeneration then affords the observed **44.3** (Scheme 46c).



Scheme 46a. Mechanism for formation of **44.2**



Scheme 46b. Mechanism for formation of **7.2**

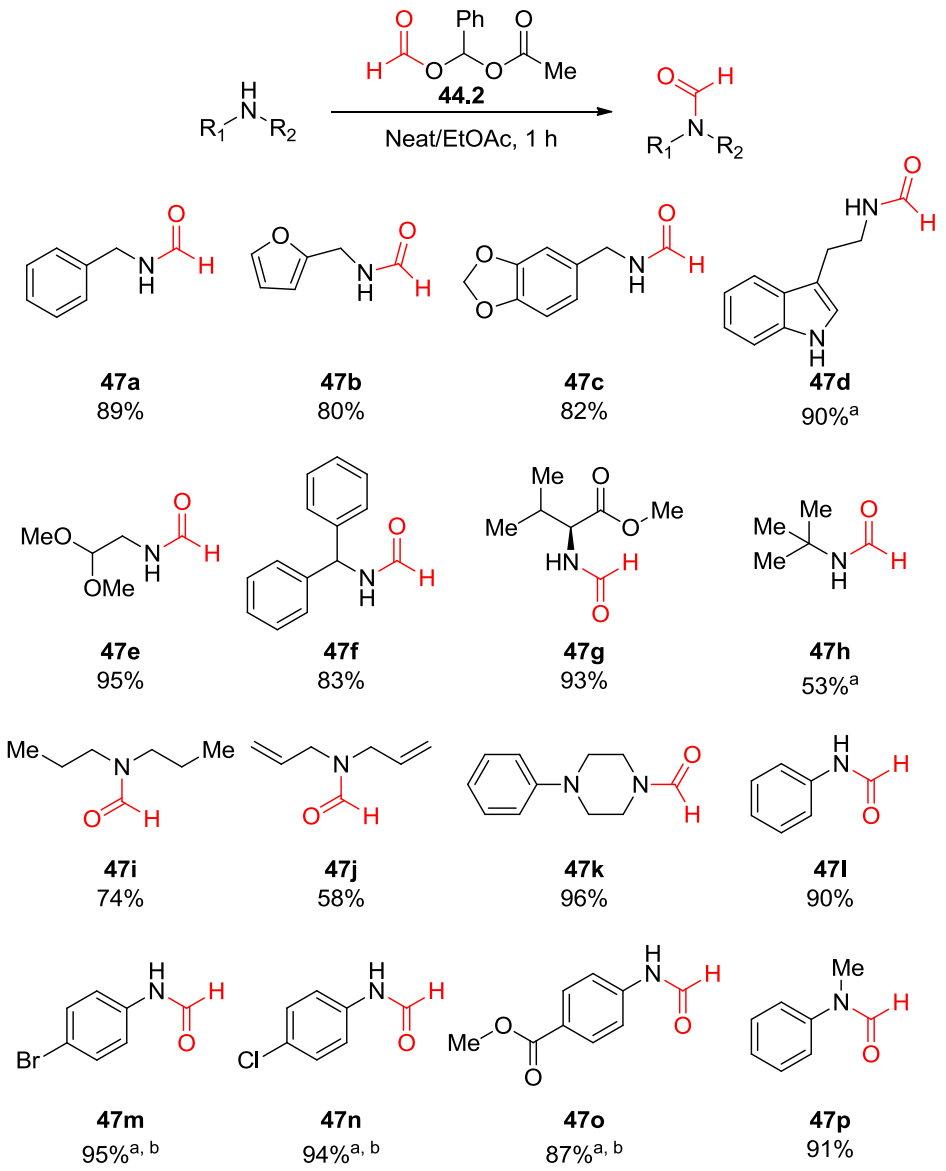


Scheme 46c. Mechanism for formation of **44.3**

Scheme 46. Mechanism for formation of mixture of products **44.2**, **7.2** and **44.3**

Pure (formyloxy)(phenyl)methyl acetate **44.2** was then applied as an *N*-formylating reagent for amines. Pleasingly, (formyloxy)(phenyl)methyl acetate **44.2** proved to be highly selective for *N*-formylation reactions, providing good to excellent yields for *N*-formylation of a range of 16 primary and secondary amines, with no evidence of any competing acyl transfer occurring. These formylating reactions afforded a range of 16 formamides **47a-p** in 53-95% isolated yields. Again, the reactions were able to be purified directly *via* column chromatography, without the need for an aqueous work up. For non-volatile products, removal of by-products could be achieved by distillation under high vacuum. It is also worth noting that due to the increased reactivity of this formylating agent, these reactions could be carried out at rt, with the reaction time reduced to just 1 h (Scheme 47).

When tryptamine was used as a substrate there was no evidence of competing formamide formation at the indole nitrogen (**47d**). It is also important to note that when (*S*)-valine methyl ester was formylated, there was no evidence of any racemization of its stereocentre (determined by alpha D for **47g**, $[\alpha]_D^{20} = -22$; Lit = -23.45[85]), which is often a problem with other acylating reagents. The low yield of tert-butylformamide **47h** can be ascribed to the steric hindrance of the amine and the volatile nature of both the starting amine and product formamide. A range of electron deficient anilines were also successfully formylated **47l-p**, including the sterically hindered *N*-methyl aniline that gave formamide **47p** in 91% yield. In some instances where the amine was not soluble in the formylating reagent, EtOAc was added as a co-solvent leading to significantly longer reaction times.



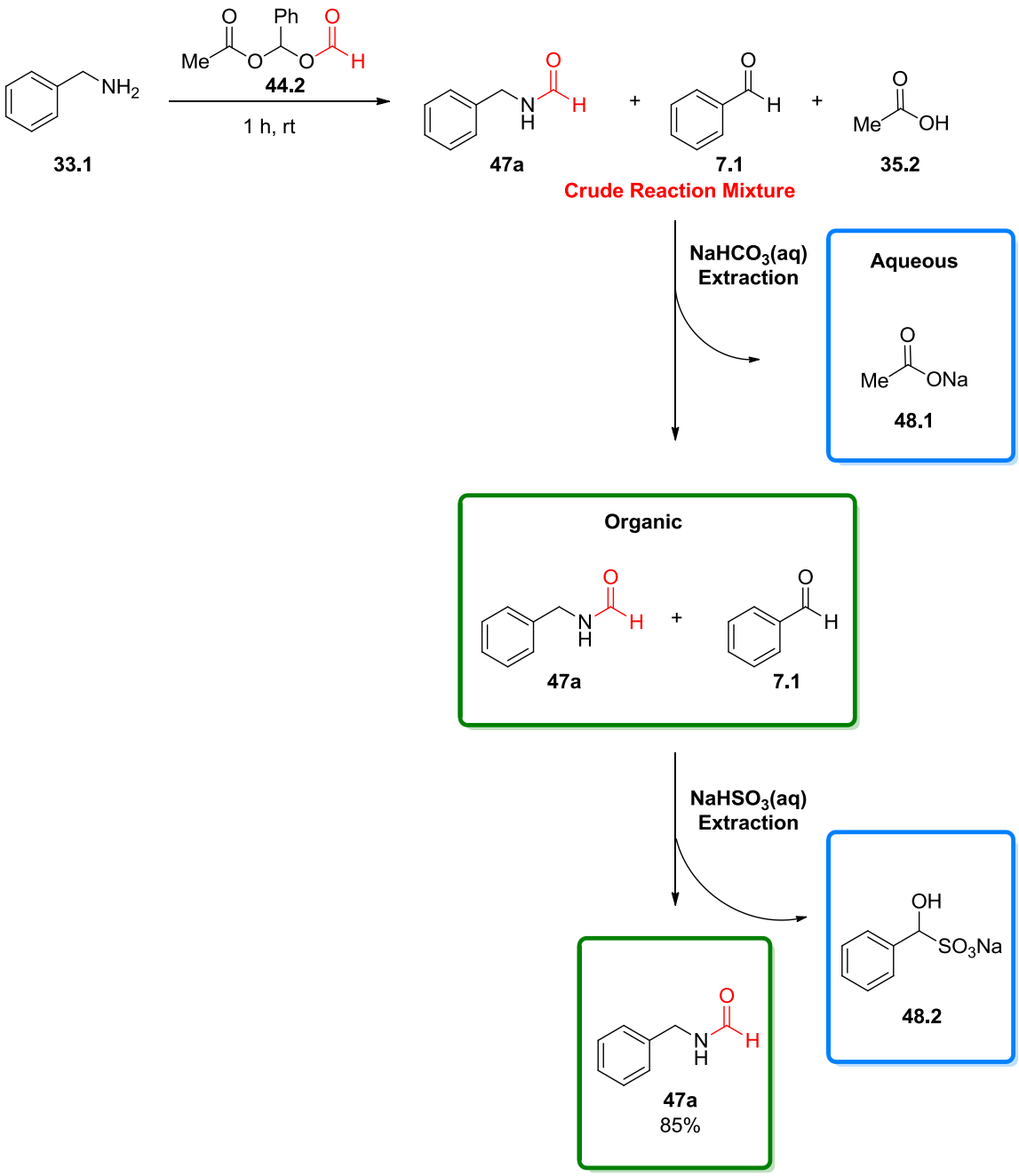
Reaction conditions; 2 mmol of amine, 1.5 equiv.**43.2**, 1 h, rt. [a]EtOAc required as solvent. [b]24 h reaction time.

Scheme 47. N-formylation reactions of amines using acylal **44.2**

1.61 An *N*-Formylation Reaction Performed on Scale

The *N*-acylation and *N*-formylation reactions described in previous sections were all purified *via* column chromatography, however, this kind of purification approach is clearly not compatible to process scale-up. With potential large scale application of these reagents in mind, it was decided to develop an alternative purification route that would not rely on chromatography. It was found that when the desired amide or formamide products were

crystaline, or oils with a suitably high boiling point, then both the acetic acid and benzaldehyde by-products could be easily removed by distillation *in vacuo*. However, when this approach was not a viable option (e.g. for volatile **47j**), an aqueous work up with saturated $NaHCO_3$ could be used to remove the acetic acid, followed by extraction with a solution of saturated $NaHSO_3$ that removes the benzaldehyde by-product as its water soluble bisulfite adduct. For example, this purification approach was performed on a crude formylation product produced from reaction of 5g of benzylamine **33.1** with 9.06 g of formylation agent **44.2** under standard conditions. ^{1}H NMR spectroscopic analysis revealed that the reaction afforded a mixture of the desired *N*-benzylformamide **47a**, benzaldehyde and acetic acid. An aqueous work up with $NaHCO_{3(aq)}$ resulted in removal of sodium acetate **48.1**. Secondly, a bisulfite extraction then allowed for removal of benzaldehyde as its bisulfite adduct **48.2**, affording 5.36 g of *N*-benzylformamide **47a** in a slightly reduced 85% yield (Scheme 48).



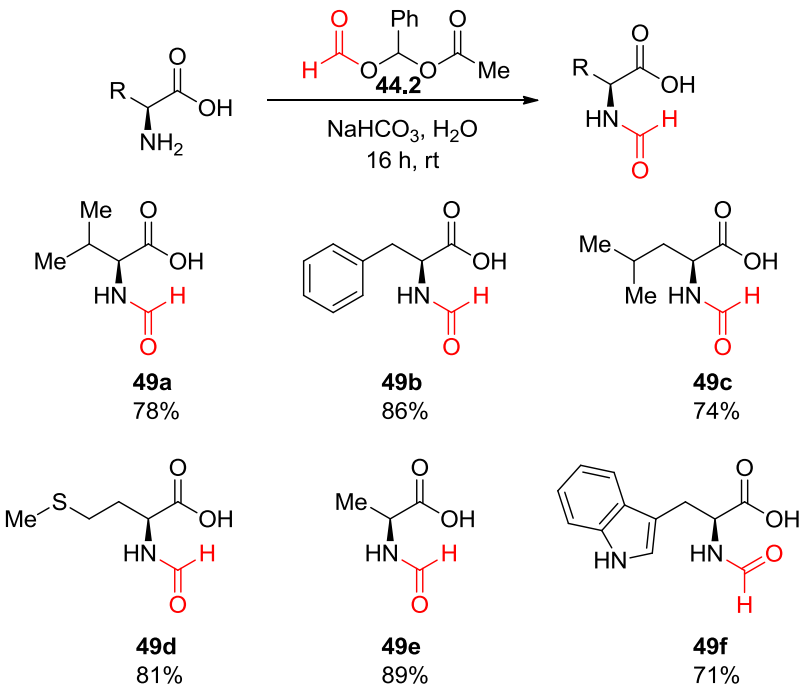
Scheme 48. Chromatography free purification of a large scale *N*-formylation reaction of benzylamine

1.62 *N*-Formylation Reactions of Amino Acid and Peptides

1.621 *N*-Formylation Reactions of α-Amino Acids

The direct *N*-formylation of unprotected α-amino acids remains an attractive goal in organic synthesis with only a limited range of synthetic protocols currently available.[76, 80, 86, 87] One of the main issues arises from the poor solubility of amino acids in organic solvents and the incompatibility of many formylating reagents with water, which may act as a competing

nucleophile. Of the synthetic protocols that are available for *N*-formylation of unprotected α-amino acids, the formyl source is either formic acid or formamide, both of which have a high tolerance to water. We observed that reagent **44.2** was relatively resistant to hydrolysis by water, and therefore it was decided to attempt the direct *N*-formylation of unprotected α-amino acids using water as a solvent. Pleasingly, it was found that (formyloxy)(phenyl)methyl acetate **44.2** could be used for *N*-formylation of α-amino acids under aqueous conditions. Formylation conditions were optimized for these α-amino acid substrates resulting in the use of 5 equivalents of $NaHCO_3$ as a base, extended reactions times of 16 h, and addition of a second 1.5 equivalents of (formyloxy)(phenyl)methyl acetate **44.2** after 8 h. This resulted in *N*-formylation of unprotected amino acids proceeding to afford a range of six *N*-formyl α-amino acids **49a-f** with good to excellent yields 71-89% (Scheme 49). The purification of *N*-formyl α-amino acids was performed using an aqueous $NaHCO_3$ wash to remove the acetic acid and any unreacted amino acid. This was followed by recrystallization of the crude *N*-formyl-α-amino acid from a mixed solvent system of EtOAc and pentane. Comparison of the $[\alpha]_D^{20}$ of **49a-f** with those of literature revealed no evidence of any racemization having occurred. These type of *N*-formyl amino acids have found numerous applications; for example through conversion to isocyanides as substrates for multicomponent reactions, and their use in peptide synthesis.[88]

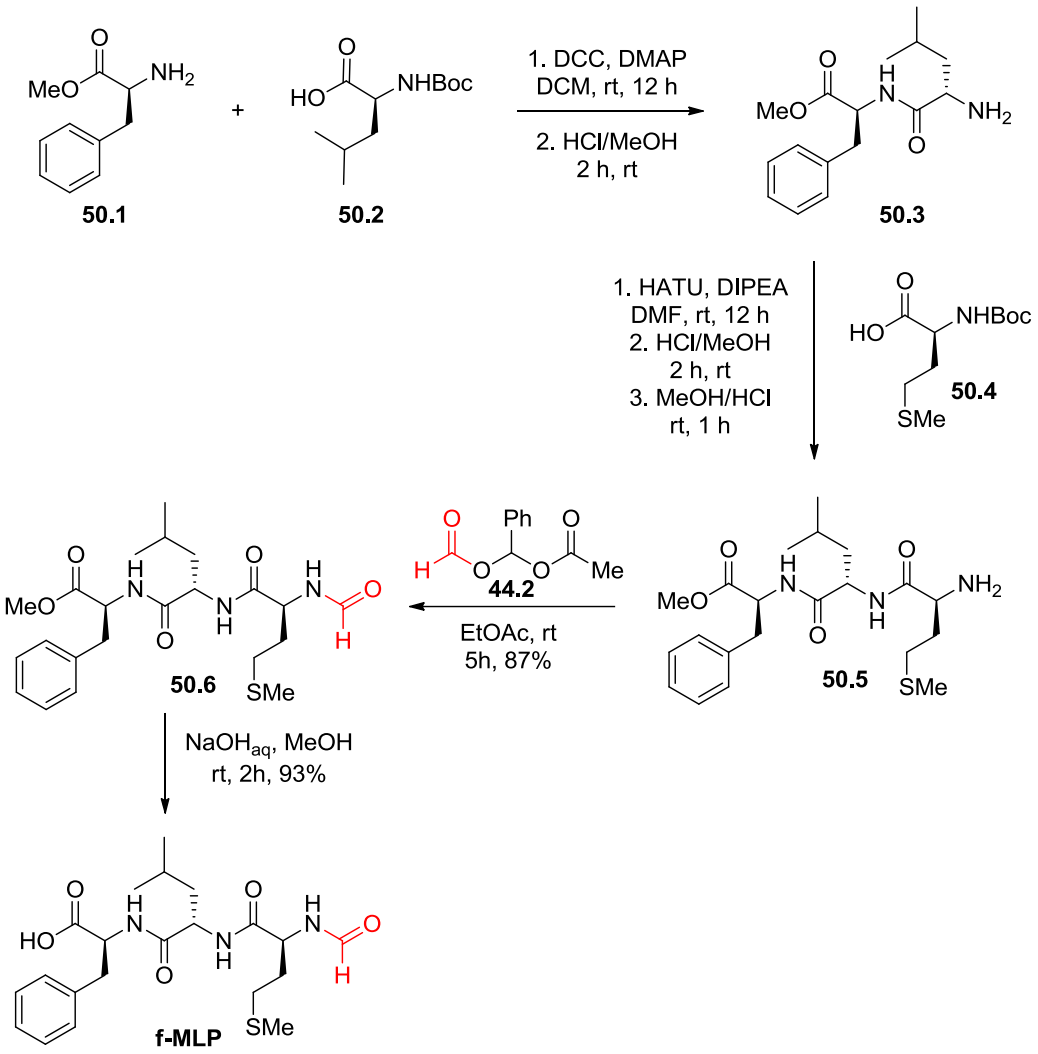


Reaction conditions; 1 mmol of amino acid, 1.5 equiv **44.2**, 5 equiv $NaHCO_3$ 16 h, rt (after 8 h 2nd 1.5 equiv. of **44.2**).

Scheme 49. N-formylation of unprotected amino acids.

1.622 *N*-Formylation of Peptides

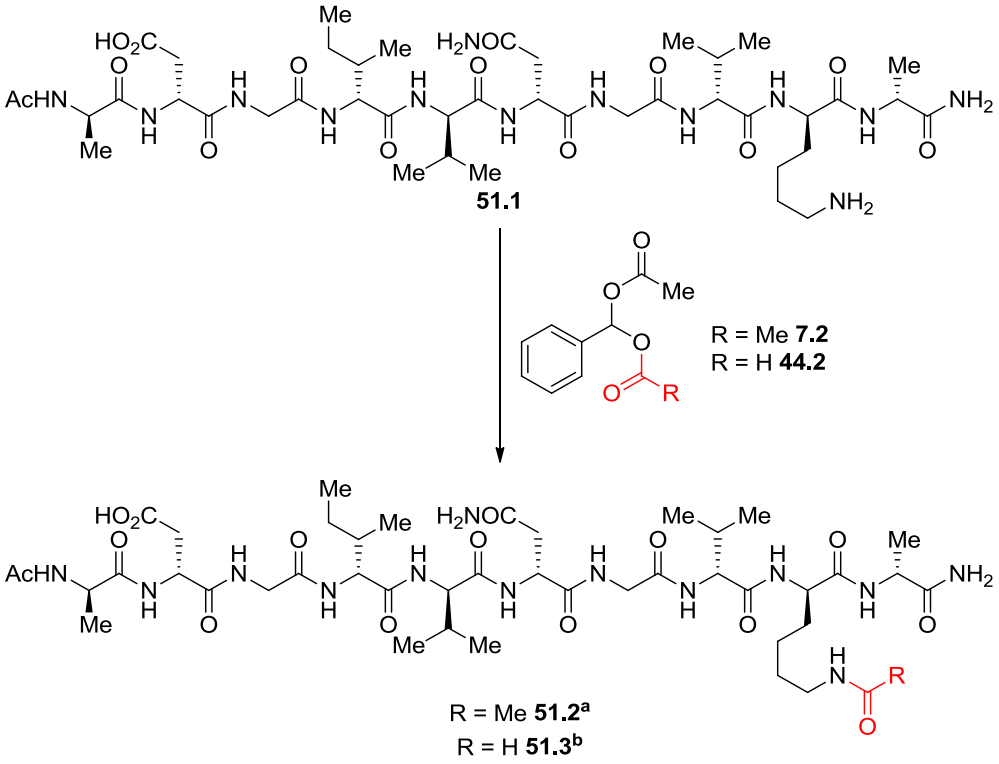
Formylation is not only used extensively in peptide synthesis as a protecting group, there are a number of naturally occurring and synthetic peptides which contain a formamide group that are essential for their biological activity.[89] One of the best known examples is *N*-formylmethionyl-leucyl-phenylalanine (f-MLP), which is a potent polymorphonuclear leucocyte chemotactic factor and macrophage activator.[89-91] F-MLP has been used extensively in biological and medicinal research,[90, 91] therefore its synthesis was identified as a challenging substrate to test the scope and limitation of formylating agent **44.2**. The tripeptide **50.5** was first synthesized according to literature,[92] dipeptide **50.3** was formed using DCC coupling of phenylalanine methyl ester **50.1** and *N*-Boc leucine **50.2**, followed by *N*-Boc-deprotection using methanolic HCl. A HATU facilitated amide bond formation reaction was then carried out between dipeptide **50.3** and *N*-Boc methionine **50.4** to afford the desired *N*-boc protected tripeptide, which upon treatment with methanolic HCl resulted in tripeptide **50.5**. This tripeptide was then treated with formylating reagent **44.2** in the presence of EtOAc as a co-solvent to afford *N*-formyl tripeptide **50.6** in 87% yield. Subsequent ester deprotection through base hydrolysis then afforded f-MLP in 93% yield (Scheme 50).



Scheme 50. Synthesis of f-MLP.

It was then decided to further test the limitations of these reagents as formylating and acylating agents, for the ω-amino residue of a lysine residue of a more complex peptide. A small amount of decapeptide **51.1** with the sequence Ac-ADGIVNGVKA-NH_2, whose N-terminus protected as an acetamide and whose C-terminus was protected as a primary amide, was acquired from Dr Jody Mason (Department of Biology and Biochemistry, University of Bath). This peptide was reacted with both the acetylating and formylating reagents **7.2** and **44.2** with the aim of selectively acylating the free ω-amino group of its lysine residue. Previous control experiments had demonstrated that neither of these reagents could acylate or formylate primary amides. The acylation conditions used were altered slightly to accommodate the other amino acid residues present in this peptide. To ensure that the ω-amino group of the lysine residue was present as its free amine, the reaction was buffered at pH 8. The co-solvent system

used was a mixture of MeCN, H_2O and a few drops of DMSO. Satisfyingly, both acetylating and formylating reactions proceeded to successfully produce formamide peptide **51.2** and acetamide peptide **51.3**. Formation of both peptide products was confirmed by the presence of the correct molecular ions for **51.2** (HRMS (ESI): m/z calculated for $C_{44}H_{74}N_{13}O_{15}$: requires: 1025.5433 for $[M-H]^-$; found: 1025.5483) and **51.3** (HRMS (ESI): m/z calculated for $C_{43}H_{73}N_{13}O_{15}$: requires: 1010.5276 for $[M-H]^-$; found: 1010.5292) in their HRMS respectively (Scheme 51).



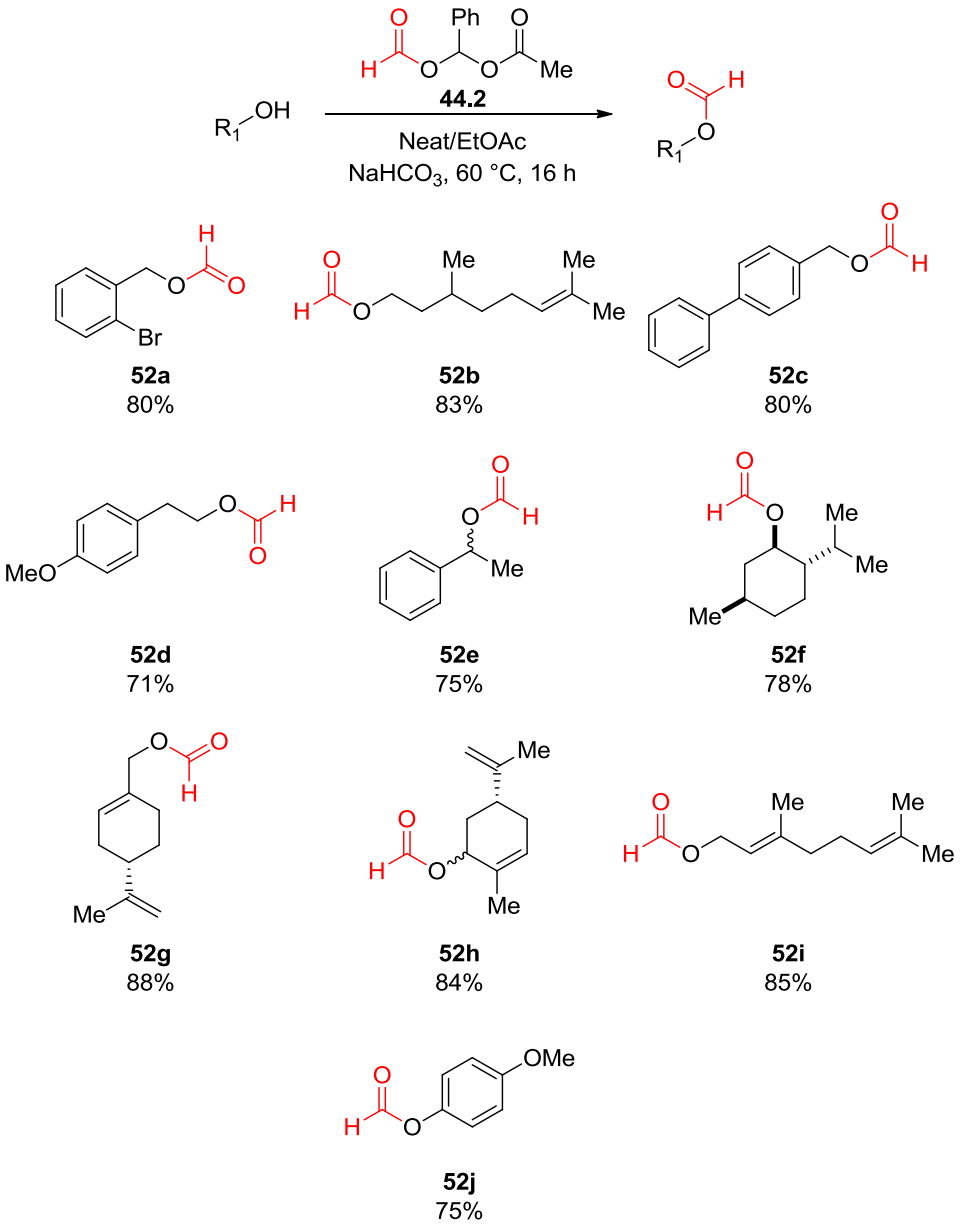
Reaction conditions; [a]5 equiv **7.2**, MeCN/H_2O/DMSO pH 8, 50 °C, 24 h. [b] 5 equiv **43.2**, MeCN/H_2O/DMSO pH 8, rt, 24 h

Scheme 51. N-Acylation and *N*-formylation reactions of peptide **51.1**

1.63 *O*-Formylation Reactions of Alcohols

The corresponding *O*-formylation reactions of a range of alcohols using reagent **44.2** were then carried out, for the synthesis of a range of ten formate esters using $NaHCO_3$ as a base, at a slightly lower temperature of 60 °C. Pleasingly, these *O*-formylation reactions were compatible with a wide range of alcohols including phenols, primary, secondary and allylic alcohols, producing a range of ten formate esters **52a-j** in 71-88% yield (Scheme 52). It is known

that 4-methoxyphenyl formate **52j** is susceptible to hydrolysis due to the low pKa of its resultant phenol hydrolysis product, so an isolated 75% yield for **52j** highlights the generally mild nature of the reaction conditions.

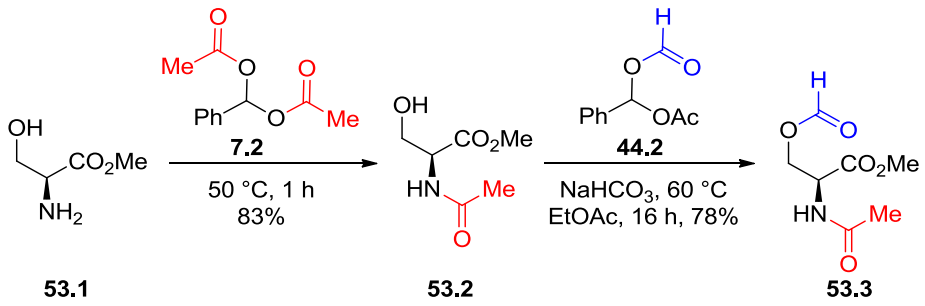


Reaction conditions; 1 mmol of alcohol, 1.5 equiv. **44.2**, 2 equiv. $NaHCO_3$, 16 h, 60 °C. [a]24 h reaction time.

Scheme 52. O-formylation reaction of alcohols.

1.64 Investigation into the *N-/O-* Selectivity Profile of Acylals

The *N-/O-* selectivity profile of these acylating/formylating agents was then investigated utilizing serine methyl ester **53.1** as a bifunctional test substrate. *N*-acetylation was performed under neutral conditions using acylal **7.2** to selectively give *N*-acetyl-serine methyl ester **53.2** as the sole product in 83% yield. *O*-formylation was then conducted using reagent **44.2** under the standard basic conditions to give *N*-acetyl-*O*-formylserine methyl ester **53.3** in a 78% yield, with no evidence of any *N-/O*-acyl scrambling having occurred, a phenomenon which has been documented previously using acylated serine substrates (Scheme 53).[93] There was also no evidence of racemization which can be a concern when using protected amino acid esters (determined by alpha D, $[\alpha]_D^{20}$ = -9.5; Lit = -10.1[94] **53.2**, $[\alpha]_D^{20}$ = +56 **53.3**). When these reactions were attempted in alternative order (formylation followed by acetylation), *N*-formylation of serine methyl ester **53.1** proceeded well, however, the relatively high temperature required for *O*-acetylation led to decomposition of the formamide starting material.



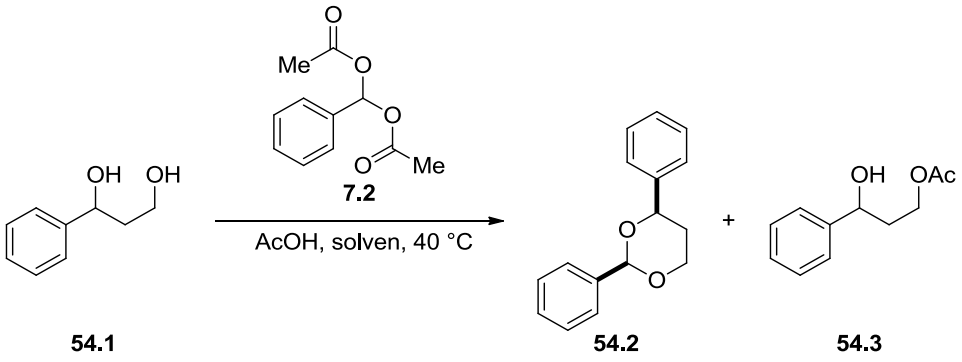
Scheme 53. N-/O-selectivity demonstration with serine methyl ester

1.7 Acetalisation of 1,2-Diol and 1,3-Diol Utilizing Acylals

In order to further explore the reactivity and utility of acylals it was decided to assess their reactivity towards diols under acidic conditions for the potential synthesis of cyclic acetals. Reactions to afford acetal and ketal groups are highly important reactions in organic synthesis, where they are often used to reversibly protect the functionality of carbonyl groups. This is particularly prevalent in natural product syntheses, which often utilize multiple acetal and ketal forming reactions to protect diols present in synthetic intermediates. In these more complex systems it is important to have mild reaction conditions to introduce the acetal protecting group as many natural product intermediates contain functionality that are not stable to strong acids,

or high temperatures. It was proposed that phenylmethylene diacetate **7.2** might serve as a useful reagent for the protection of diols as their cyclic benzaldehyde acetals.

An initial reaction was performed involving reaction of phenylmethylene diacetate **7.2** with 1-phenyl-1,3-propandiol **54.1** in CH_2Cl_2 using a catalytic amount of acetic acid (Scheme 54). The reaction proceeded at rt, to afford a modest conversion of 30% for formation of acetal **54.2**, along with a significant amount of monoacetate **54.3** (10%). This was a promising result that warranted further optimization, and so a solvent screen was conducted with the results presented in Table 3. Five solvents were screened with acetonitrile and dichloromethane, entries 2 and 3, giving the best results, showing 85% and 80% conversion to acetal **54.2** respectively. Unfortunately formation of monoacetate **54.3** could not be completely suppressed (Table 3), however, it is worth noting that the cyclic acetal was formed with total *syn*-diastereoselectivity under these conditions, with no evidence of any *anti*-diastereomer being present.



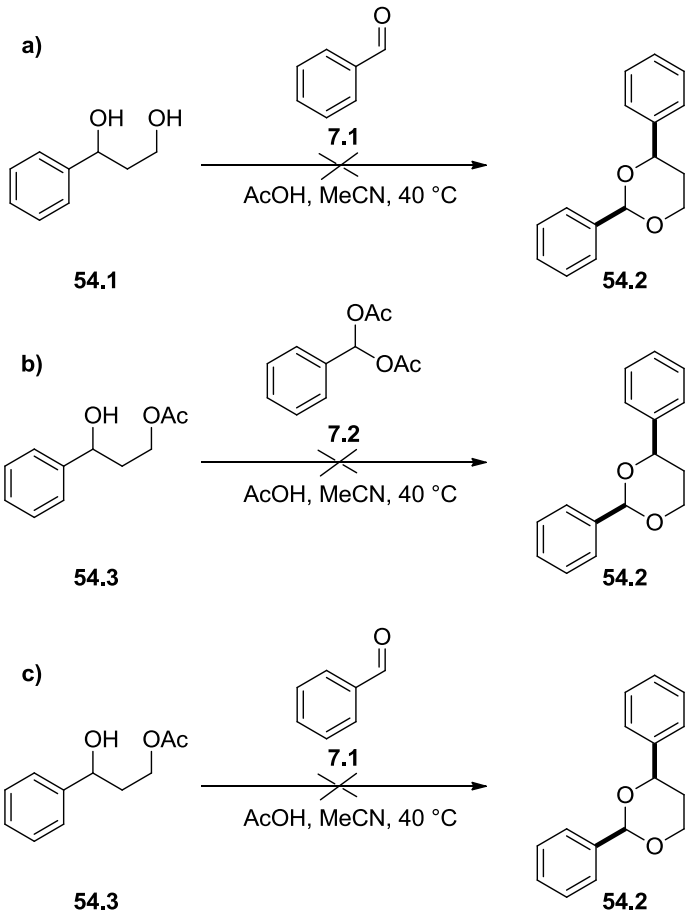
Scheme 54. Acetal protection of diol **54.1**

Table 3. Solvent screen for the optimisation of acetal protection of diol **54.1**

Entry	Solvent	Monoacetate 54.3 (%)	Acetal 54.2 (%)
1[a]	Dichloromethane	10	30
2	Toluene	9	7.5
3	Acetonitrile	13	85
4	Dichloromethane	10	80
5	Ethyl Acetate	32	5
6	Hexane	31	66

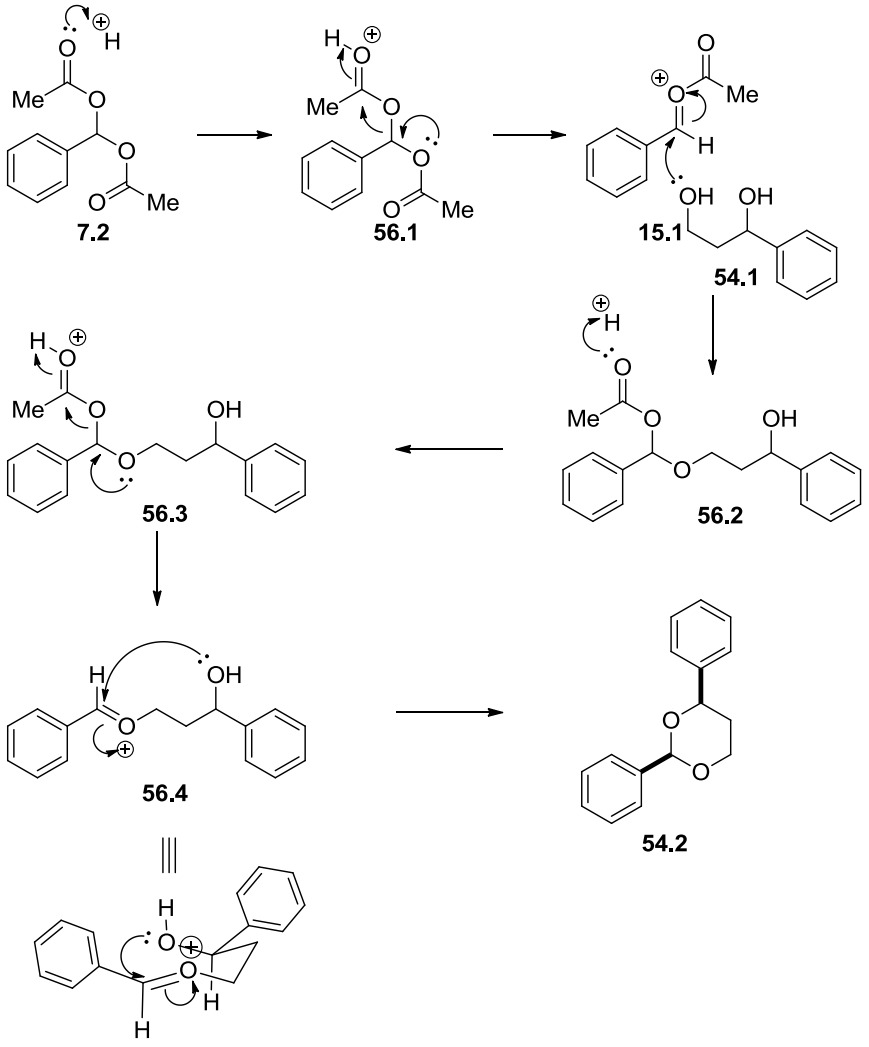
Reaction conditions; 0.5 mmol of diol, 5 equiv. **7.2**, 1 mol% AcOH, 3 mL solvent, 12 h, 40 °C a = rt.

In order to investigate the mechanism of this acetalisation reaction a number of control experiments were conducted, with some of the key reactions carried out shown below (Scheme 55). Firstly, it was important to show that benzaldehyde was not acting as the acetalising agent under these conditions, since acid catalysed breakdown of phenylmethylene diacetate **7.2** could afford benzaldehyde **7.1**, which could potentially undergo a normal acid catalyzed acetal protection reaction. Pleasingly, as shown in reaction **a)**, no acetal product was produced when benzaldehyde **7.1** was substituted in place of acylal **7.2**. We next determined whether monoacetate **54.3** might be an intermediate in the reaction pathway. Therefore, monoacetate **54.3** was synthesised separately (from reaction of diol **54.1** with acetic anhydride, isolated from a mixture of products) and subjected to the standard reaction conditions. As shown in reaction **b)**, these conditions afforded no evidence of any acetal formation. Finally, reaction of monoacetate **54.3** with benzaldehyde **7.1** in the presence of acetic acid in MeCN at 40 °C (reaction **c**), once again gave no evidence of any acetal formation (Scheme 55).



Scheme 55. Reactions to investigate the mechanism of acetal **52.2** synthesis

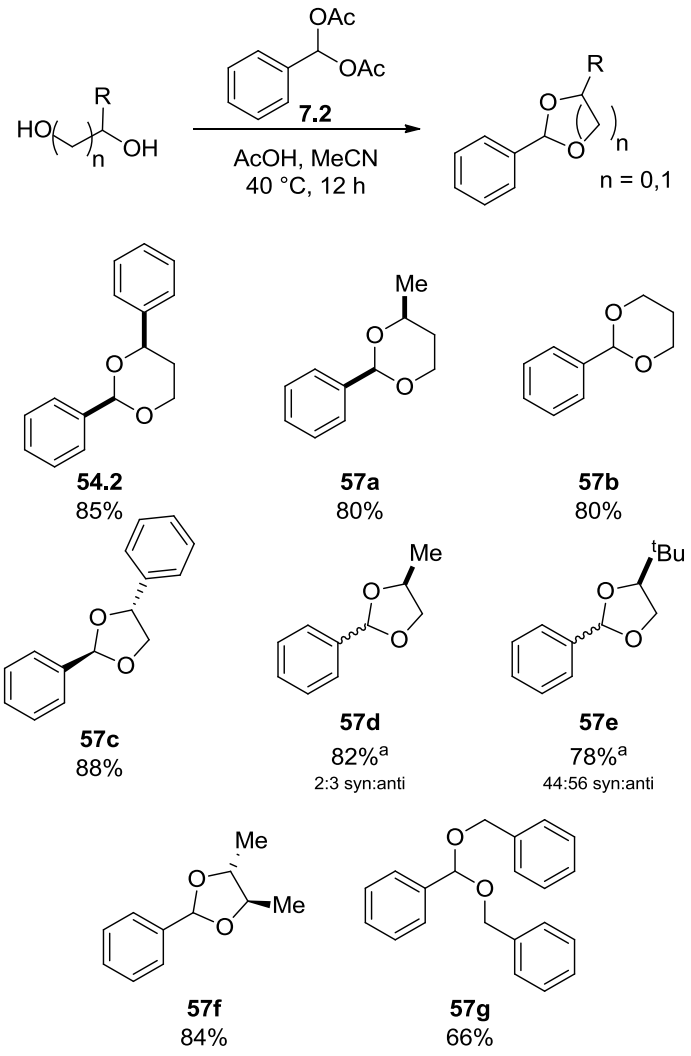
Given these results, the reaction is proposed proceed *via* initial protonation of acylal **7.2** to afford oxonium **56.1**, with elimination of one of its acetate groups to produce *O*-acyl oxonium species **15.1**, which is then primed for nucleophilic attack of the primary alcohol functionality of diol **54.1** to give acetate **56.2**. A second protonation step then occurs to give oxonium **56.3**, which eliminates a second acetate group to produce alkyl oxonium **56.4**. Intramolecular attack of the free secondary hydroxyl group of **56.4** then leads to formation of the desired cyclic acetal **54.2** (Scheme 56).



Scheme 56. Proposed mechanism for the formation of acetal **52.2**

It was then decided to investigate the substrate scope of this new acetal protection protocol. A small selection of seven 1,2-diols and 1,3-diols were protected as their benzylidene acetals, using acylal **7.2** as the acetalising agent in acetonitrile at 40 °C, in the presence of a catalytic amount of acetic acid. These acetalisation conditions were applied to a range of diols to afford a range of cylic acetals **54.2**, **57a-f** in 66-88% yield, including substrates containing methyl, phenyl and the sterically demanding tert-butyl group. Again, where enantiopure diols **57c/57f** were used, the acetalisation reaction proceeded without racemization ($[\alpha]_D^{20}$ = -100 **57f**; $[\alpha]_D^{20}$ = -33; Lit = +32[95] (opposite enantiomer) **57f**) (Scheme 57). The 1,3-diols formed 6 membered ring acetals, with *syn*-diastereoselectivity, whereas 1,2-diols formed 5 membered ring acetals predominantly with *anti*-diastereoselectivity.

The majority of the reactions proceeded to afford a single diastereomer, however, acetals **57d** and **57e** were isolated as a mixture of *syn/anti* diastereomers. Importantly, acylal **7.2** could also be used for the synthesis of acyclic acetals such as acetal **57g**, albeit with a slight reduction in yield when using the alcohol substrate as the limiting reagent.

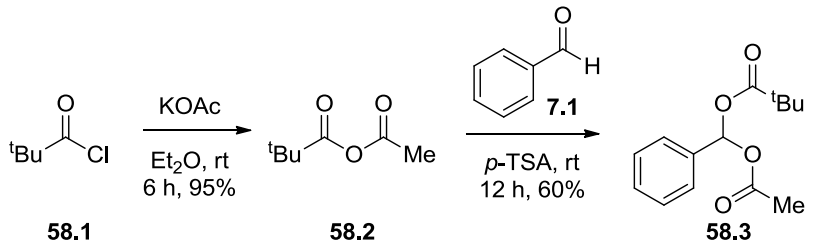


Reaction conditions; 1 mmol of diol, 3 equiv. **7.2**, 1 mol% AcOH, 3 mL solvent, 12 h, 40 °C. [a]Product isolated as a mixture of diastereomers.

Scheme 57. Acetal protection of diols

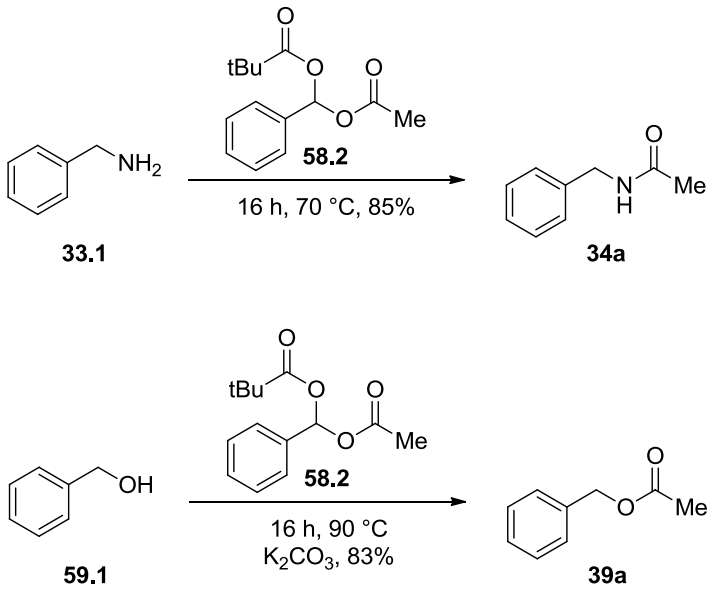
1.8 Preliminary Investigations into the use of Mixed Acylals for *N-/O*-Acylation Reactions

One area where this project could be advanced is through the use of a mixed acylal reagent that contains a sterically hindered pivaloyl whose steric bulk would ensure that it was not transferred as an acyl group. This would allow for the selective transfer of the acyl group of choice, allowing for a much more efficient process, especially if a valuble and complex acyl group needs to be transferred. Synthesis of a mixed acylal was performed in the same way as for the preparation of (formyloxy)(phenyl)methyl acetate **44.2**, substituting *O*-formaylacetate **44.1** for acetic pivalic anhydride **58.2**. Reaction of this mixed anhydride with benzaldehyde **7.1** gave the desired mixed acylal acetoxy(phenyl)methyl pivalate **58.3** in 60% yield (Scheme 58).



Scheme 58. Use of mixed *gem*-diacetate for selective acyl transfer

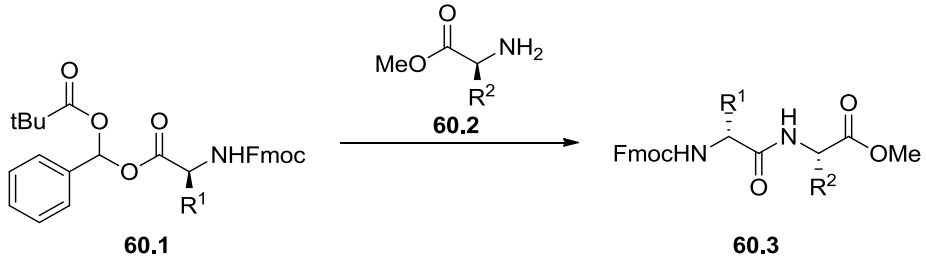
Two preliminary experiments were carried out to determine whether this approach was viable using acetoxy(phenyl)methyl pivalate **58.2** as the acylating agent, in the hope that the acetate group would be transferred, due to the steric bulk of the *tert*-butyl group preventing nucleophilic attack at its proximal carbonyl. Pleasingly, these reactions proceeded well, affording the desired acetamide **34a** in 85% yield, and the corresponding acetate ester **39a** in a 83% yield, with no evidence of any *N*-benzylpivalamide or pivalic ester being formed (Scheme 59). It is anticipated that this type of mixed acylal reagent will have the most impact, where a more complex or expensive acyl group needs to be transferred. However, due to time constraints this area could not be fully explored, and further experiments to explore the scope and limitation of this approach will be carried out in the near future.



Scheme 59. Preliminary example of selective acyl transfer

1.9 Future Work

There are a number of potential routes where this project could be taken forward. A key area would be to fully explore the use of mixed acylals for acylation reactions. One potential powerful application could be the use of a mixed acylal for peptide synthesis. For example, acylal **60.1** containing a protected amino acid fragment could be used as an acylating agent for a range of amines, with acylation of an amino acid methyl ester **60.2** potentially enabling facile dipeptide synthesis (Scheme 60).



Scheme 60. Proposed use of mixed acylals for peptide synthesis

These mixed acylals could also be potentially used for labelling the amine/alcohol groups of serine/lysine residues of proteins with fluorophores, allowing the targeted protein to be visualised within the cell. Labelling using a mixed acylal should be selective for tagging only

those residues that are solvent exposed on the surface of the protein. Which should mean that the labelling event should not affect the protein activity. Furthermore, transfer of acyl units containing alkyne functionality would allow for “click” chemistry to be carried out to modify protein surfaces, or for immobilising proteins to surfaces.

Another exciting area where acylals could be applied is as potential suicide inhibitors (pro-drugs). There are a number of drug molecules which contain aldehyde functionalities. However, while this aldehyde functionality accounts for the impressive biological activity they possess, it also results in some highly undesirable side effects, usually caused by the toxicity related to the high reactivity of an aldehyde group towards nucleophile in a cellular environment. One such drug is MG-132 which is a specific, potent, reversible, and cell-permeable proteasome inhibitor (Figure 5). MG-132 activates c-Jun N-terminal kinase (JNK1), which initiates apoptosis, allowing for its use in anti-cancer therapies.

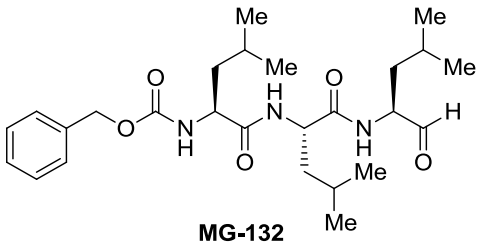
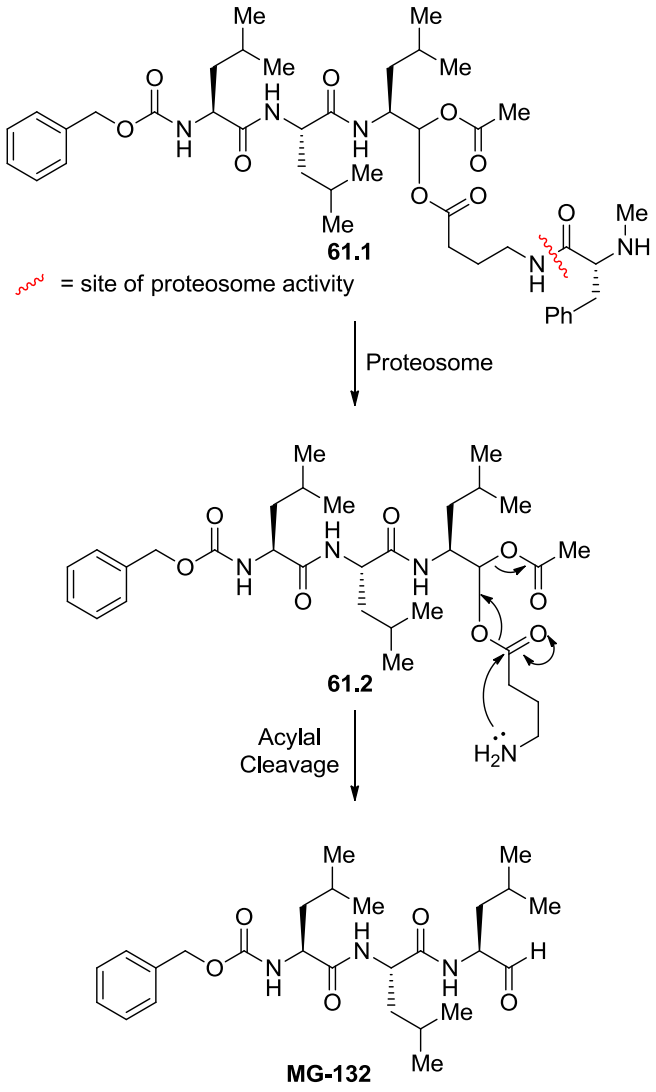


Figure 5. MG-132

One way in which the toxicity of this compound could be reduced is to mask the aldehyde as an acylal. This acylal could be designed in such a way that the aldehyde functionality is only revealed in cells that contain high levels of cell activity (cancer cells which also have an acidic pH which would also accelerate acylal clevage). Proteasome cleavage of the phenyl alanine motif present in acylal **61.1** could potentially lead to the generation of free amine **61.2**. This amine would then be able to undergo an intramolecular acylation causing the elimination of acetate and generation of the aldehyde functionality of the parent compound MG-132 (Scheme 61).



Scheme 61. Potential use of acylal methodology for the design of a suicide inhibitor

1.10 Conclusion

In conclusion a new branch of reactivity has been discovered for acylals which had previously been shown to exhibit a wide range of reactivity towards a range of nucleophiles.[31, 35-39, 41-46] We have shown them to be highly active reagents for the *N*-/*O*-acylation of amines and alcohol nucleophiles for the synthesis of a range of formamides, acetamides, formate esters and acetate esters. It has been demonstrated that a range of acyl groups can be transferred including short and long chain alkyls, acryloyl, benzoyl, phenyl acetyl and biologically important trifluoroacetyl group, thus enabling the synthesis of a range of benzylamides and esters. These acylation reagents have also been shown to demonstrate inherent *N*-/*O*- selectivity towards the amine and alcohol groups of serine methyl ester.

To explore further the scope and limitations of these reagents (formyloxy)(phenyl)methyl acetate **44.2** has been applied for the *N*-formylation of a range of unprotected amino acids, and for the synthesis of the biologically important tripeptide f-MLP. As well as this, both phenylmethylene diacetate **7.2** and (formyloxy)(phenyl)methyl acetate **44.2**, have been applied for the acylation/formylation of the ω-amino residue of a lysine residue within a decapeptide. Finally, it has also been demonstrated that a simple switch in pH from basic to acidic conditions for diols can change from *O*-acylation to acetal formation.

In conjunction with the research described above, work was also been carried out towards A protecting group free strategy for the sustainable synthesis of polyketide natural products and their analogues. An introduction into this area will now be presented.

2.0 Efficient Natural Product Synthesis

2.1 Introduction

Throughout documented human history chemical substances derived from natural sources; plants, animals and microbes have been utilised as medicines in the treatment of diseases and ailments.[96] However, the first chemical synthesis of a natural product did not occur until 1828 with the synthesis of urea from inorganic ammonium cyanate by Wöhler.[97, 98] Wöhler demonstrated that natural products, despite being derived from living organisms, could also be synthesised in the laboratory.[98] This breakthrough led to the first targeted synthesis of an "organic " natural product; acetic acid in 1884.[98, 99] Up until the 1960's, natural product synthesis was predominantly a tool to either confirm, or decipher the structure of the natural product under investigation. Common spectroscopic techniques taken for granted today were either in their infancy, or yet to be discovered; i.e. UV/vis spectroscopy (1930's), Infra-Red spectroscopy (1940's) and perhaps the most important, nuclear magnetic resonance (NMR) (1950's). Before this, the total synthesis of a complex molecule from known building blocks to give the proposed structure was one of the best methods of structural determination and confirmation. A comparison of physical properties with an isolated genuine sample of the natural product was then used to confirm that the correct compound had been assigned/synthesised.[98]

3.0 Early Natural Product Synthesis

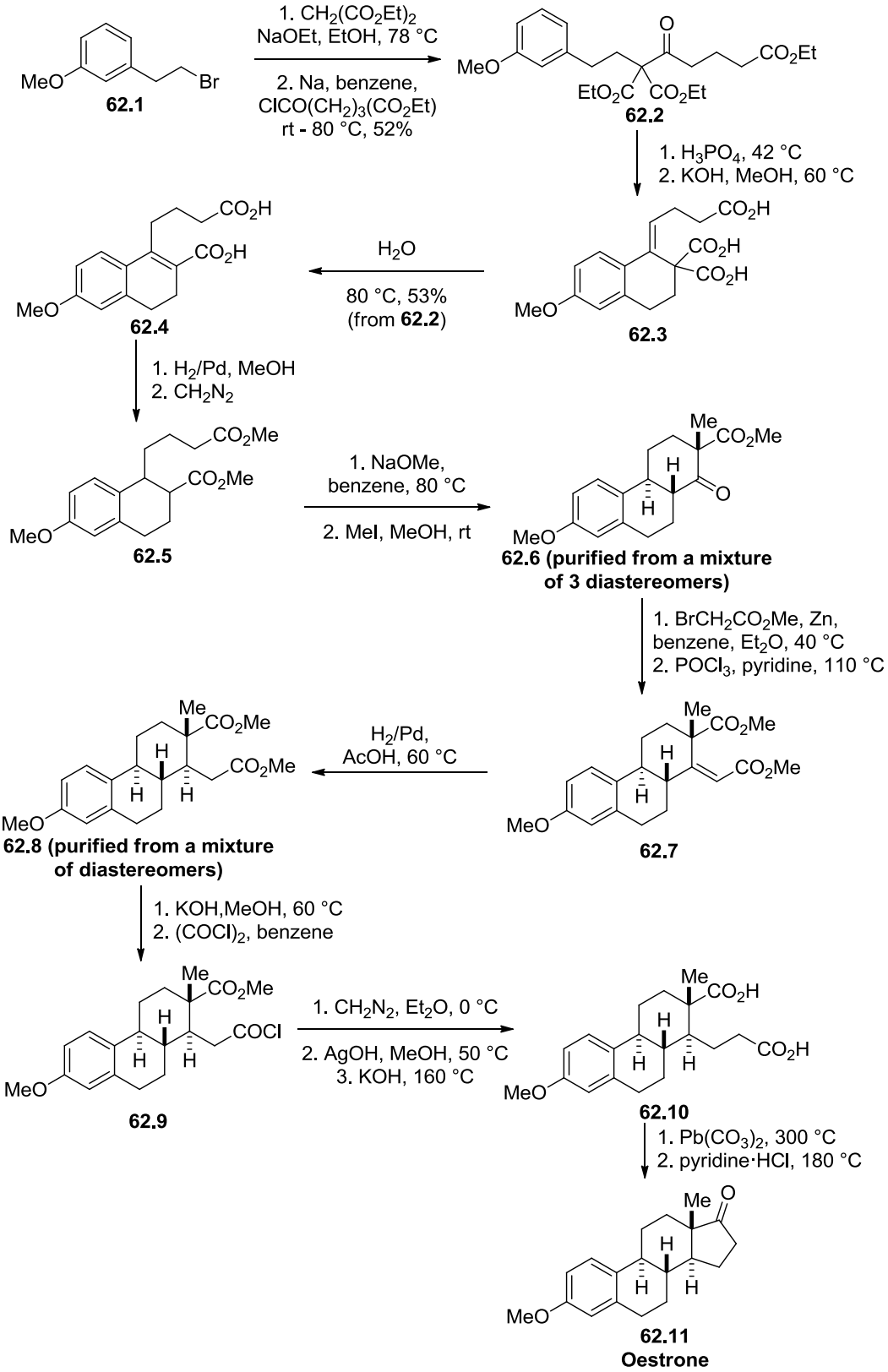
An example of early natural product synthesis is the relay synthesis of oestrone; which relied on a combination of synthetic techniques from Robinson,[100] Bachmann,[101] Anner and Miescher.[102] The synthesis shown in Scheme 62 is known as a "relay", because it targets a known intermediate that could also be generated from degradation of the natural product. For example, ketone **62.6** had been previously isolated through the degradation of oestrone, and a synthesis of oestrone from ketone **62.6** had been established.[98, 100] The synthesis shown is typical of the time: the molecular skeleton is formed using reactions that only introduce small changes to the overall structure, maintaining a level of control over the desired product, and increasing the likelihood that the predicted transformation would occur. This concept relied heavily on the use of established skeletal building reactions, resulting in natural product synthesis at the time not employing many new "risky" reaction steps.[98] In the synthesis of oestrone, the main skeletal building step was introduction of malonic ester fragment, followed by *C*-acylation of the malonate intermediate to give ketone **62.2**. This intermediate then underwent a series of

hydrolysis, cyclisation and elimination reactions to give the diacid **62.3**. Decarboxylation of diacid **62.3** then occurred, with alkene bond migration affording the more thermodynamically stable tetra-substituted alkene **62.4**. Alkene hydrogenation, followed by esterification generated bis-ester **62.5**, which underwent Dieckmann cyclisation to afford bis-ester **62.5**, whose enolate was methylated to give β-keto-ester **62.6**. However, **62.6** was formed as one of three racemic diastereomers, which needed to be separated by fractional crystallisation. A Reformatsky reaction on the desired diastereomer, followed by dehydration of the resultant β-hydroxyester, afforded α,β-unsaturated ester **62.7**. Alkene hydrogenation, followed by further fractional crystallisation purification of the resultant mixture gave the pure diester of diastereomers **62.8**. Formation of acyl chloride **62.9** was followed by Arndt-Eistert homologation to afford C1-homologated ester **62.10**, which was then cyclised/decarboxylated to afford oestrone **62.11**. At the time the Arndt-Eistert homologation was a relatively new reaction, so its inclusion as a key step at a late stage of a natural product synthesis was considered quite revolutionary. Only the yields for the first four steps are available, therefore comments about overall yield cannot be made.

While it may seem unfair to compare this synthesis to modern day efforts, by so doing it can help demonstrate how far synthesis has evolved over the years, and highlight areas where progress is still lacking. Key features of this oestrone synthesis are:

- Atom economy = 15%
- 9 Functional Group Interconversion (FGI) steps, including a number of ester hydrolysis/esterification steps
- 2 reductive steps
- Lack of stereocontrol during the cyclisation and hydrogenation steps
- Use of toxic $Pb(CO_3)_2$ as a base
- Use of toxic/explosive diazomethane in the C1-homologation reaction

An atom economy of 15% for the synthesis of a complex molecule is relatively good, however a more strategic synthetic plan might have resulted in a number of the inherently inefficient functional group interconversion (FGI) steps being avoided. A number of reagents used would no longer be acceptable by modern industrial standards, $Pb(CO_3)_2$ is highly toxic and lead regents are avoided where possible, whilst carrying out the cyclisation reaction at 300 °C seems excessive. Diazomethane is toxic but also presents an explosion risk, while the use of these reagents was common place, a greater awareness of health and safety might result in an alternative flow protocol being considered for this step.



Scheme 62. An early pioneering synthesis of oestrone[98]

It is important to remember that during these early years of synthesis, how limited the synthetic "tool box" was, with many fewer reactions being available for consideration for natural product synthesis. This is particularly highlighted in the creation of stereogenic centres where the ability to control steroselectivity in a reaction was much less well developed, often resulting in low yielding formation of complex mixtures of racemic diastereomers that were difficult to purify.

The success or failure of natural product syntheses at this time relied heavily on the choice of the original starting material, which meant that each synthesis was 'bespoke' relying on a level of intuition from the chemist.[98, 103] This level of "intuition" is well illustrated in the total synthesis of homoeroquinene reported by Woodward and Doering in 1945 (Scheme 63).[98, 104] This achievement generated a lot of interest, both within the scientific community and the wider population. This was due to the therapeutic properties of quinine for the treatment of malaria, which had become an acute problem, due to the British, Dutch and French Empires having expanded their influence into malaria infected territories.[98, 103]

This synthesis was again a relay synthesis based on the work of Kindler[105] and Prelog,[106] who had isolated quinotoxine and homoeroquinene from the degradation of quinine, and subsequently demonstrated that quinine could be reconstructed from these compounds (Figure 6).

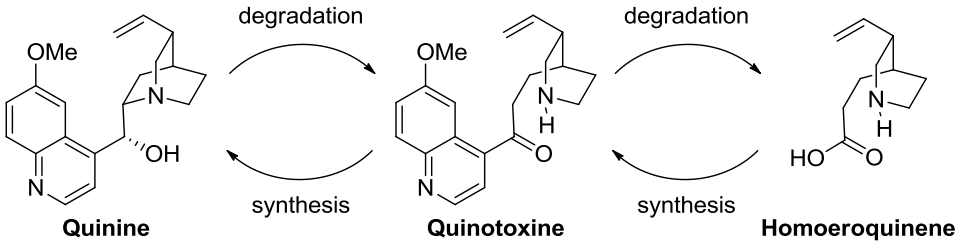


Figure 6. Structural relationship between quinine, quinotoxine and homoeroquinene[98, 105, 106]

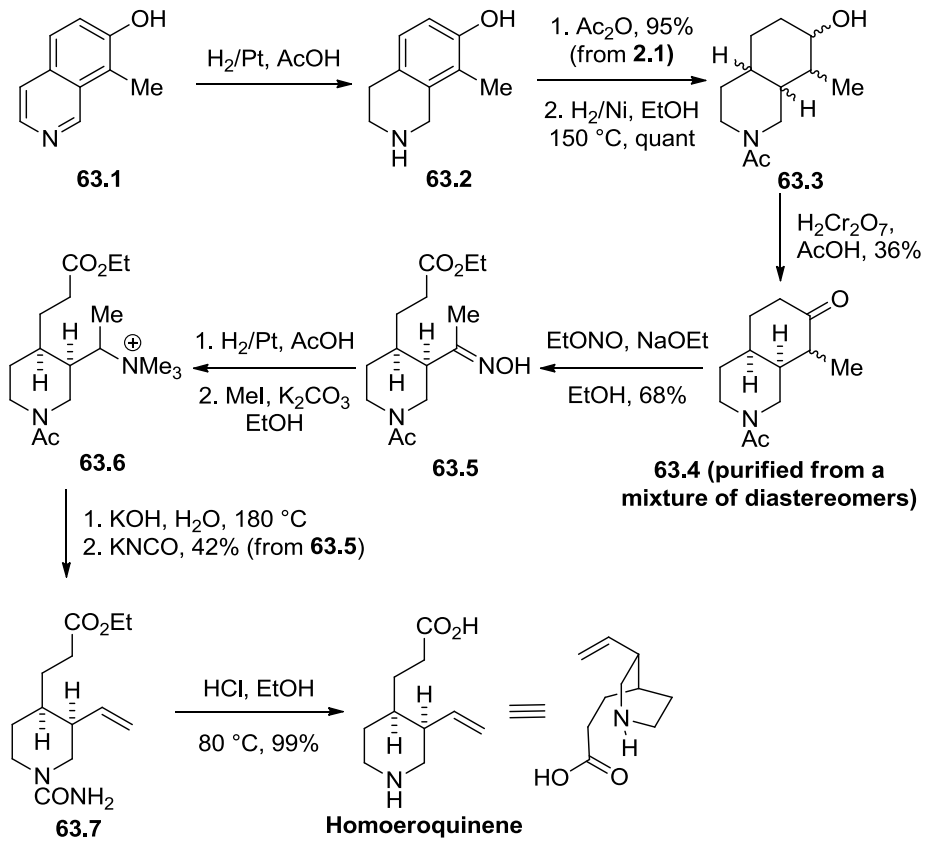
The choice of the hydroxyquinoline **63.1** as the starting material highlights the shrewd thinking of Woodward, as all of the skeletal atoms required for the desired intermediate homoeroquinene were already in place from the offset.

Initially, the nitrogen containing ring of the hydroxyquinoline **63.1** was selectively hydrogenated to give hydroquinoline **63.2**. *N*-Acetylation followed by de-aromatisation gave the

fully saturated hydroquinoline **63.3**. Complete control over the facial selectivity of the hydrogenation of **63.2** to give the desired *cis* arrangement was unsuccessful and therefore after oxidation to ketone **63.4** a separation of diastereomers was required. The cyclohexanone ring was then oxidatively cleaved with ethoxy nitrite to give oxime **63.5**, which was subsequently reduced and *N*-methylated to give the quaternary ammonium salt **63.6**. Hofmann elimination resulted in selective alkene formation followed treatment with potassium isocyanate to give urea **63.7** (required for purification), which after acid catalysed hydrolysis of both its urea and ester functionalities gave the desired homoeroquinene (Scheme 63).

Key features of this homoerquinene synthesis are:

- Atom economy = 17%
- 10 steps, 10% overall yield from **63.1**
- 2 oxidation steps (including use of stoichiometric chromium oxidants)
- 3 reductive steps
- Poor stereocontrol during the hydrogenation step
- Creation and then destruction of 2 stereocentres



Scheme 63. Woodward and Doering synthesis of homoeroquinene.[98, 104]

With the development of modern day analytical spectroscopic techniques (UV/vis, IR and NMR) and with X-ray crystal structure analysis becoming the established techniques for structure elucidation, Synthetic organic chemists were suddenly free to explore more ambitious syntheses. This new freedom for natural product synthesis was perhaps best captured by Eschenmoser.[98, 107]

"Elimination of the classical function of providing structural proof for natural products implied liberation from the restriction that only very well established reactions may be applied in a synthesis. Natural product synthesis henceforth provides a challenge to invent and to develop novel reactions and to discover novel reactivity patterns."

However, developments in the art of the synthesis were not purely about developing new reactions, since access to new reactivity profiles also enabled increasingly complex natural product targets to be prepared. These synthetic breakthroughs allowed many new drug molecules to be prepared, as well as enabling chemical probes to be synthesised that enabled biochemical pathways to be interrogated.[108] As soon as a new complex natural product was

isolated, then the race was on to achieve its total synthesis, with the research groups of internationally renowned scientist such as Danishefsky, Evans and Nicolaou, (and numerous others), having achieved impressive syntheses of many different of highly complex natural products.

This change in direction led to large surge in natural product synthesis research culminating in a peak in output during the 1970-90s.[96, 98, 108, 109] This increase in interest had a dramatic impact on the pharmaceutical industry during this time, with 49% of the 877 new molecular entities introduced as drugs between 1981-2001 being derived from natural product leads. Indeed this percentage increases further when two of the most crucial therapeutic areas are considered; with natural product inspired leads responsible for 60% of the drug molecules approved in the areas of anti-cancer and anti-infection during the period 1984-1995.[96, 110-113]

3.1 Natural products as drug molecules

The inherent biological activity, high structural diversity and specificity profiles of the large number of natural products that have been isolated, means that they may be considered to be privileged lead molecules for drug discovery purposes.[96, 108, 114] However, the complexity of many natural products often makes them difficult to modify chemically, which is often required when the pharmacokinetic properties of the parent natural product need to be modified. Natural products are also often not available in sufficiently large enough quantities from renewable natural sources. Instead, advances in increasing the efficiency of synthetic organic chemistry protocols are still needed, to help remove perceived barriers associated with using natural product derived lead compounds in drug discovery programs.[114] Indeed, one of the main driving forces in modern natural product synthesis is to develop new reaction protocols that address efficiency/sustainability issues, and demonstrate that they can be applied to the synthesis of structurally complex structures.[108]

A prominent example of the type of problems that are often faced, is for the multigram total synthesis of the potent anticancer marine polyketide natural product (*+*)-discodermolide carried out by Merck process chemists in collaboration with Paterson and co-workers.[115-119] The demand for this compound could not be met through isolation from its natural source; a marine sponge *Discodermia sp.,*[115] with repeated attempts to culture *Discodermia sp.* expressing the correct symbiotic microorganisms that produce discodermolide having proven unsuccessful to date. Therefore, a viable synthetic route to large mulitigram quantities of discodermolide was required, with the first total synthesis by the Schreiber group requiring a 32 step synthesis in

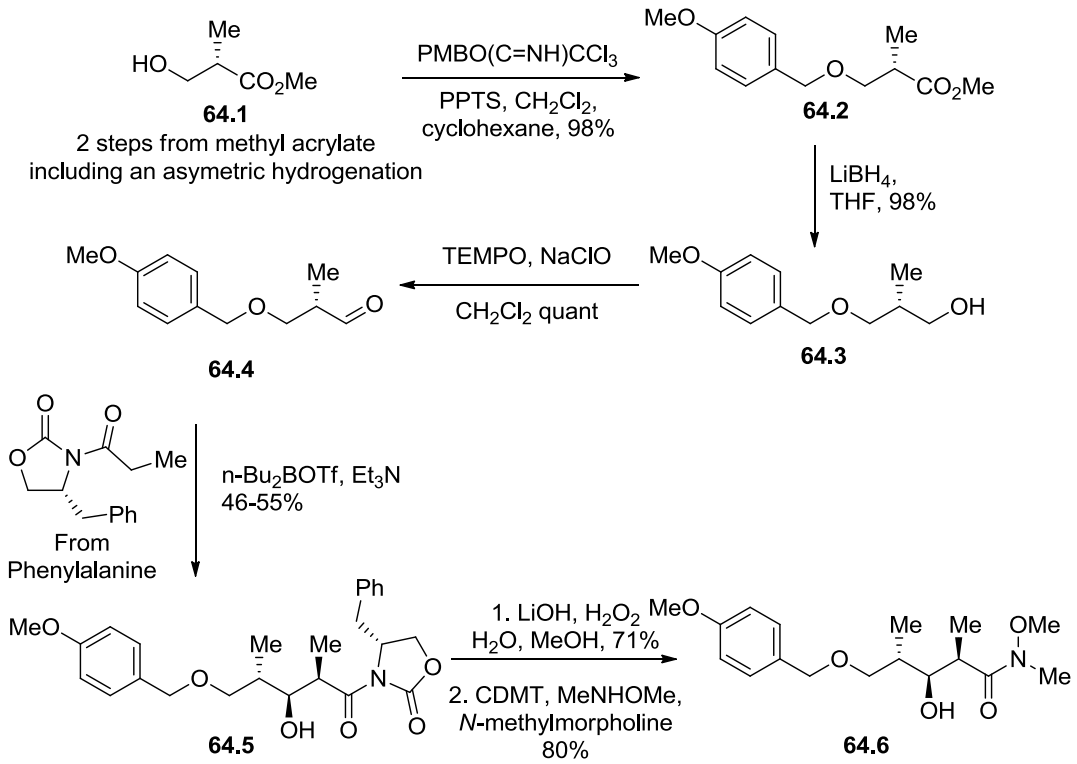
only 3.2% overall yield.[120] While an impressive example of natural product synthesis, the low yield rendered this route unviable for the production of (*+*)-discodermolide on a large scale, and as a consequence a new more scalable route was required. Many attempted improvements were made to increase the yield of its synthesis,[121-127] with the semi-industrial route that was eventually devised for the synthesis of multigram quantities of (*+*)-discodermolide ultimately being a hybrid of previous syntheses.

Initial efforts focused on the production of the common Weinreb amide intermediate **64.6** which had been identified as a key synthon by Smith in an earlier synthesis.[121-123] This route begins with the readily available Roche ester **64.1** which was first *O*-protected as its *p*-methoxy-benzyl ether **64.2**. Upon reduction, alcohol **3.3** was obtained which was readily oxidised *via* a TEMPO oxidation to give aldehyde **64.4**. This aldehyde **64.4** was then reacted with the boron enolate of a chiral *N*-acyl-oxazolidin-2-one to afford an Evans *syn*-aldol product **64.5**. The aldol product **64.5** was purified by recrystallization, hydrolysed, and then subjected to Weinreb amide formation using the coupling reagent CDMT. This sequence of reactions gave Weinreb amide **64.6** in six steps, in large quantities (1.6 kg) and required no chromatographic purification steps (Scheme 64).[115]

While this route was clearly compatible for synthesis on a medium scale, there are still, a number of areas in which the synthesis of this fragment could be improved. Roche ester **64.1** is a commercially available starting material, however, at a cost of ~£20/g for the (*S*) isomer and ~£30/g for the (*R*) isomer, it is perhaps not the best choice as starting material for a large scale multi-step synthesis of a drug compound. The synthesis of intermediate **64.6** also utilises protecting group chemistry in the form of the PMB (*p*-methoxybenzyl) protecting group which accommodates for 37 wt.% of intermediate **64.6**.

Protecting group chemistry continues to be an invaluable tool for organic chemists in the synthesis of highly complex compounds, through their ability to mask the reactivity profiles of competing functional groups, which offers an increased level of security and predictability.[128] However, the use of a protecting group introduces at least two additional synthetic steps,[129] which greatly reduces the atom efficiency of the synthesis, as well as impacting overall yield, since quantitative yields are rarely possible.[128] The atom efficiency for this five step sequence from Roche's ester **64.1** to the common intermediate **64.6** is very low at only 1.33%, and it still has a PMB protecting group in place. The use of a chiral auxiliary also has a large impact on atom efficiency as it involves incorporation and removal of a stoichiometric chiral unit, although efficient recycling of the auxiliary can potentially mitigate these concerns. Furthermore, global

ester reduction of an ester group to alcohol **64.3**, followed by an oxidation step to afford an aldehyde is inherently inefficient.

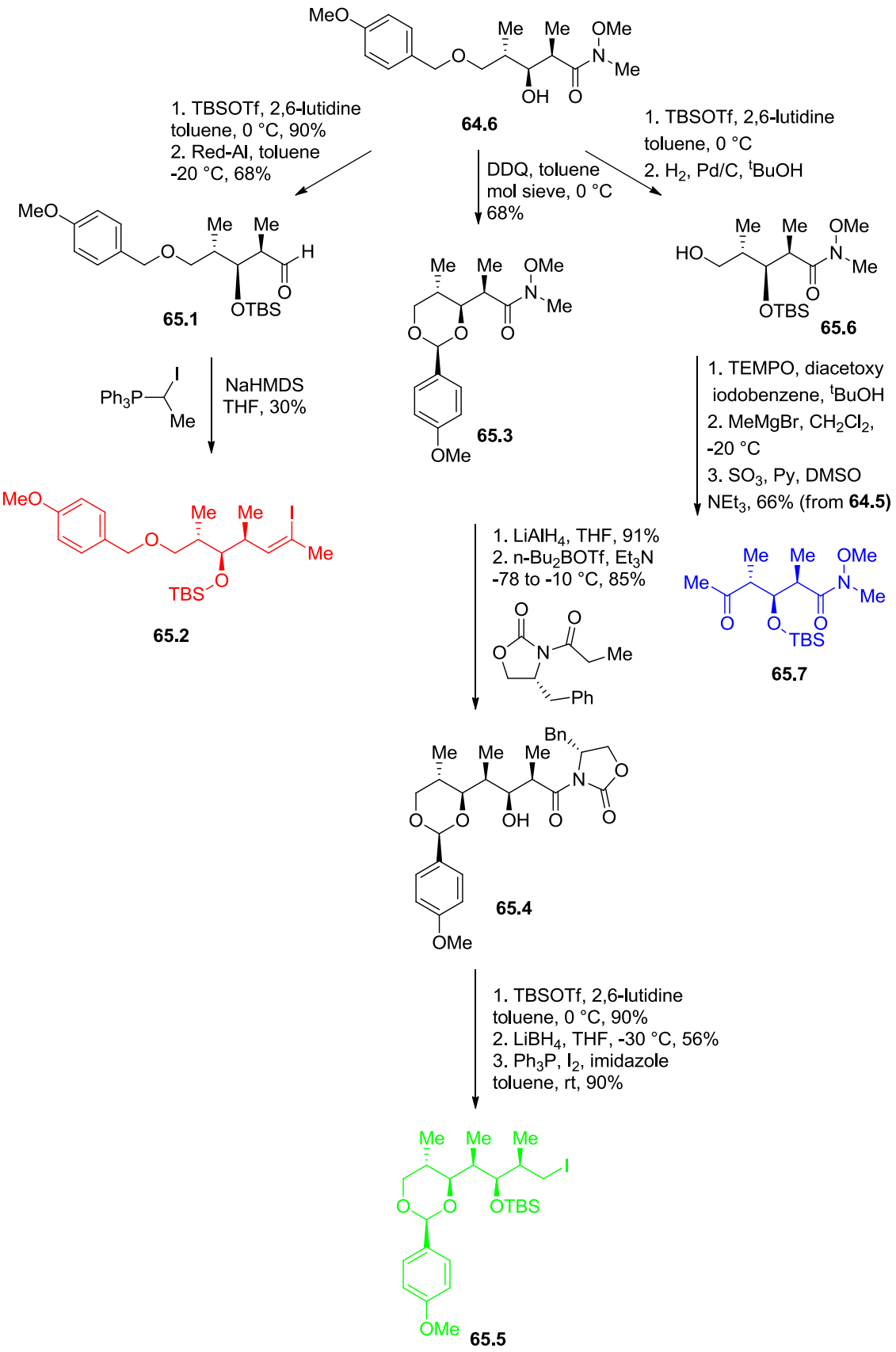


Scheme 64. Paterson et al. synthesis of common intermediate **64.6**[115]

Once intermediate **64.6** was obtained in synthetically useful quantities it was used as a core intermediate for the divergent synthesis of the three key compounds; alkene **65.2**, acetal **65.5** and ketone **65.7** in four, seven and five steps respectively.[121-123, 126, 127] Alkene **65.1** was prepared via *O*-TBS protection, and Weinreb amide reduction reactions to afford aldehyde **65.1** in 61% yield over two steps. Wittig olefination of aldehyde **65.1** using iodoethyl triphenylphosphonium ylide then gave iodo-(*Z*)-alkene **65.2** in a low 30% yield.

Acetal **65.4** synthesis began with a DDQ catalysed oxidative cyclisation reaction to form acetal **65.3**, which represents a clever way to manipulate a protecting group, whilst changing its overall oxidation state (e.g. alcohol to aldehyde). Weinreb amide reduction to aldehyde, was followed by an Evans-aldol reaction to generate *syn*-aldol **65.4**. *O*-silyl protection of **65.4**, was followed by reductive auxiliary cleavage with $LiBH_4$, with the resultant alcohol then subjected to an iodide mediated Appel reaction to afford acetal **65.5**.

Ketone **65.2** synthesis also started with a TBS protection, followed by PMB deprotection to afford alcohol **65.6.** Subsequent alcohol oxidation of **65.6** to its corresponding aldehyde, followed by Grignard addition of MeMgBr and secondary alcohol oxidation generated ketone **65.2** in 66% yield from Weinreb amide **64.6** (Scheme 65).



Scheme 65. Key intermediate synthesis

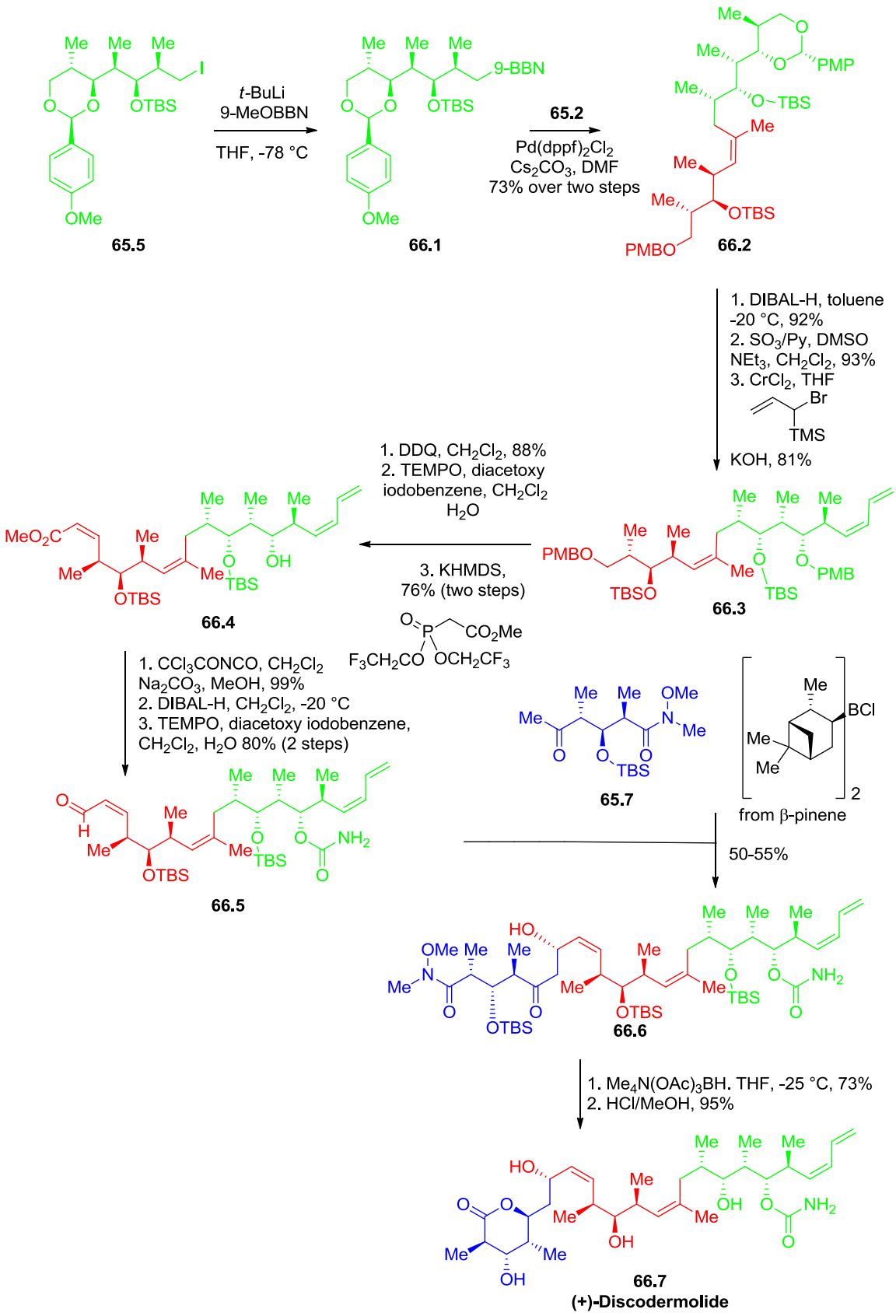
Alkene **65.2** and acetal **65.5** were then combined and functionalised in an 11 step process to give diene **66.5**. The initial reaction proceeds through metalation of iodide and reaction with 9-MeOBBN to afford borane **66.1** that underwent a Suzuki-type cross-coupling reaction with vinyl iodide **65.2** to generate trisubstituted alkene **66.2**. Selective reductive cleavage of the PMB group of **66.3** with DIBAL-H and subsequent oxidation of the resultant alcohol gave an aldehyde which was subjected to a Nozaki-Hiyama allylation reaction with 2-TMS-allyl bromide to afford diene **66.3**. Deprotection of both-PMB groups of 5.3 with DDQ, was followed by TEMPO oxidation to afford an aldehyde that was reacted with the potassium anion of bis-2,2,2-trifluoroethyl-phosphonoacetic acid methyl ester utilising a Still-Gennari variation of the Horner-Wadsworth-Emmons reaction gave vinyl ester **66.4.** The free secondary alcohol of **66.4** was derivatised with isocyanate ClCCON=C=O to afford a carbamate whose ester group was reduced with DIBAL-H followed by alcohol oxidation to afford α,β-unsaturated aldehyde **66.5** in 27% yield over 11 steps.

(*+*)-DIP-Cl boron was then used to generate the boron enolate of ketone **65.7** which underwent an aldol reaction with α,β-unsaturated aldehyde **66.5** , followed by ketone reduction, lactonization and global silyl deprotection to give the final compound (*+*)-discodermolide in a total of 39 steps, achieving a final mass of >60 g of (*+*)-discodermolide (Scheme 66).[115-119]

The synthetic steps presented in Scheme 65 and Scheme 66 follow the same general trend as those in the synthesis of common intermediate **64.6**:

- Use of numerous protection/deprotection steps;
- A series of ester reduction reactions to afford alcohol intermediates that were then oxidised to afford reactive aldehyde group;
- Use of stoichiometric amounts of chiral auxiliaries/reagents to induce stereocontrol

Finally, the question could be posed whether this synthesis could ever really be used to commercialise (*+*)-discodermolide for clinical use, since the cost of treatment would likely be too expensive to prevent its widespread use for treatment of cancer in the wider population



Scheme 66. Convergent synthesis of (+)discodermolide.[115]

Contemporary drug discovery is often based on the high throughput (HTP) screening of small molecules for biological activities associated with their ability to selectively bind to specific target proteins.[96, 98, 108] Given the limitless number of small molecule structures that are accessible for screening, it is important that chemical libraries are designed to address as broad a range of chemical space as possible, and that they contain functional groups that are biased towards biological compatibility and drug likeness. Consideration of these requirements can lead to the identification of "privileged" structures from which a whole host of compounds can then be developed for optimisation.

As mentioned earlier, natural products, can be viewed as an entire population of "privileged" structures, since they have been selected by evolutionary pressure to be able to interact with proteins, and other biological targets.[96, 114] The application of Nature's library of structures to identify lead compounds, has already led to a large number of natural products and their derivatives being used as drug compounds, a few of which are shown below. Vancomycin is a clinically relevant antibiotic; stauroporine was used as a lead compound for development of the indolecarbazole structure of anticancer drugs; rapamycin is a protein kinase inhibitor used for immunosuppression; and Taxol® is a highly potent anti-cancer drug (Figure 7).[96, 98, 108, 110-113]

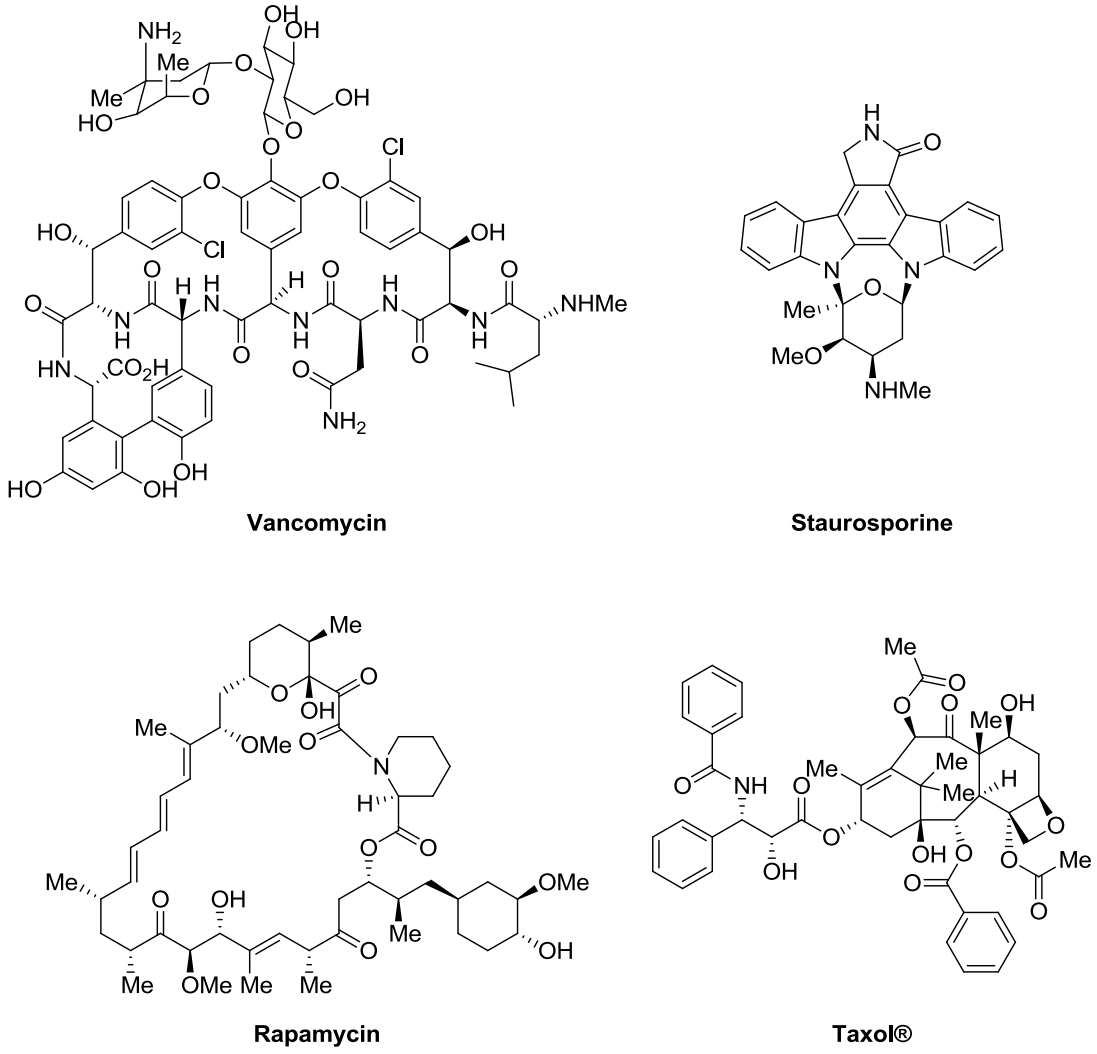


Figure 7. Natural product drug molecules[108]

Compared to purely synthetic drug molecules, natural products derived leads often have a far greater level of complexity in terms of the number of stereogenic centres, number of rotatable bonds, number of sp^3 hybridised stereogenic carbons that are present, and they often contain significantly fewer nitrogen, sulfur and halogen containing groups. They also normally contain a higher number of oxygen atoms and have a lower ratio of aromatic rings to heavy atoms when compared to their purely synthetic counterparts.[96, 108, 130, 131] Natural products are also typically larger than synthetic drugs, with molecular weights >500 increasingly common. Indeed most natural product derived drugs do not comply at all with Lipinski's "rule of five":[132] a general rule based on analysis of the structure of current drug molecules that is often used to predict the likelihood of a drug being orally bioavailable. However, despite these considerations, the current prevalence of natural product derived drugs with two or more "rule of five"

violations is still relatively low at around 10%, approximately equal to the incidence of current synthetic drugs.[96, 131, 133]

There are many challenges facing natural product synthesis in the 21st century. One of these is to push the boundaries of what many would consider to be beyond the scope of traditional natural product synthesis, with chemists becoming increasingly more daring in tackling the size and complexity of target molecules. An example of this, is the quite remarkable glycoprotein synthesis described by the Danishefsky group.[98, 134] Through targeted synthesis, Danishefsky and co-workers were able to synthesise the β-subunit of the human follicle-stimulating hormone, which is a glycoprotein with a molecular mass of 17868, setting a new benchmark for peptide synthesis.

The β-subunit of the human follicle-stimulating hormone contains 111 amino acids with two *N*-linked dodecasaccharides at Asn^{7} and Asn^{24}, with the high number of cysteine residues present in the peptide backbone allowing for the use of native chemical ligation (NCL) to assemble the protein.[135] The β-subunit was split into smaller fragments which were synthesised through Fmoc-based solid phase peptide synthesis (SPPS), with each C-terminus functionalised as a thioester ready for NCL. The cysteine residues not required for NCL were protected as acetamidomethyl (Acm) groups to prevent unwanted cross linkages being formed. The anomeric hydroxyl group of the dodecasaccharide was converted to a primary amine group using Kochetkov amination conditions, allowing for a Lansbury aspartylation reaction to be used to link the dodecasaccharide to the desired fragments. The dodecasaccharide was prepared through a highly convergent series of glycosylation reactions linking known monosaccharide building blocks. In each case, protecting groups were carefully selected to maximize stereoselectivity during glycosidic bond formation and to minimize the number of deprotection steps necessary to complete the synthesis. Subsequent deprotection and sequential NCL steps resulted in the synthesis of the β-subunit of the human follicle-stimulating hormone, which represents the largest glycoprotein to have been synthesized in a homogeneous state, using strictly chemical methods (Figure 8).[134]

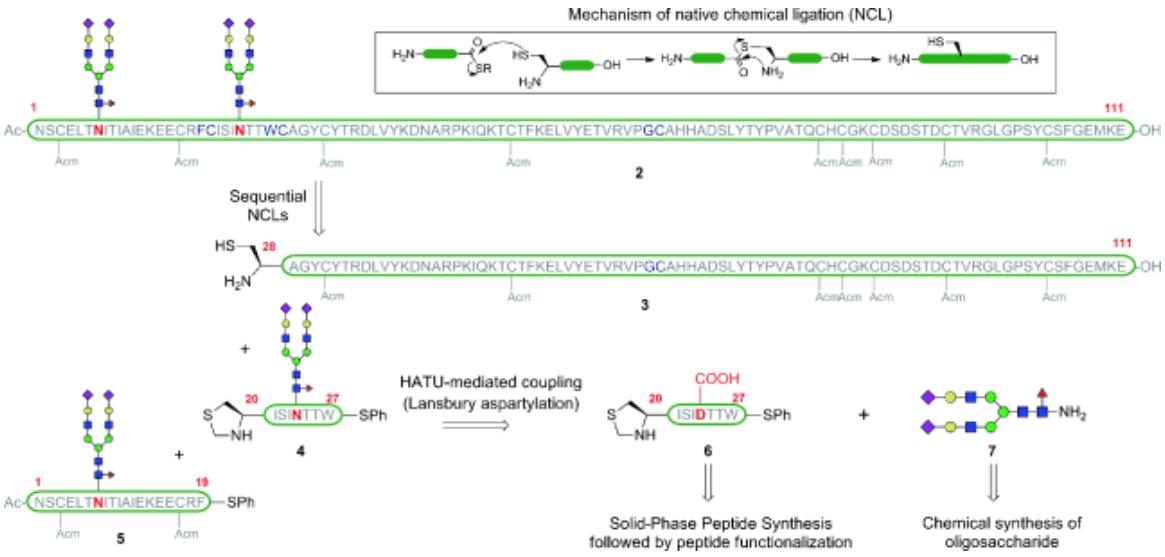


Figure 8. Retrosynthetic strategy developed by Danishefsky for the construction of the fully elaborated β-subunit of hFSH (2). HATU=O-(7-azabenzotriazol-1-yl)-tetramethyluronium hexafluorophosphate.[134]

Another area of development is the emergence of divergent total syntheses for the rapid synthesis of structurally complex lead compounds for screening purposes, which has the potential to have a large impact on the drug-discovery process. Specific intermediates generated during a natural product synthesis contain partial structural elements of the parent compound that can be used to help define which fragments of the natural product are necessary for biological activity.[136] This presents an opportunity to improve on the original compound through synthetic divergence from key intermediates,[98] whilst also interrogating which functionality is required to elicit the observed biological activity.

One example of this type of synthesis has been recently reviewed by the Taylor group.[137] They illustrated how the use of conformational-activity relationships (CAR), could be used to understand how natural products induce their biological activity, by exploring how the most active conformer of a complex natural product is bound to its biological target. This structural information could then be used to design simpler structural analogues that are easier to prepare and still demonstrate high levels of biological activity.

An impressive example of this approach has been reported for development of conformational mimics of bryostatin (Figure 9). Bryostatin is a polyketide natural product that elicits a wide array of biological responses, such as restoring apoptotic function in cancer cells, improving memory in animal models, and inducing latent HIV activation.[137] This impressive range of biological activities is believed to be due to the ability of bryostatin to activate protein

kinase C (PKC) by binding to its C1 domain. However, limited access to sufficient quantities of bryostatin has hindered its advancement into clinical trials. Synthetic techniques, while elegant, have only been successful in producing limited amounts, and isolation from its natural source is environmentally unviable (18 g of bryostatin from 40,000 L of wet bryozoan!).[137] Wender and co-workers have instead approached this problem in a different manner, using conformational analysis of bryostatin to gain an understanding of how it binds to PKC. They then employed this information to propose structural changes to bryostatin that would simplify its synthesis, whilst maintaining biological activity.[138-140] Their work culminated in the synthesis of a salicylate analogue of bryostatin (Figure 9), which still bound to PKC in low nanomolar concentrations, approaching the affinity of bryostatin itself. As is evident from considering the two structures, the salicylate analogue of bryostatin is synthetically a lot easier to access, resulting in this compound being used as a promising lead for further functionalisation and development.[137, 139]

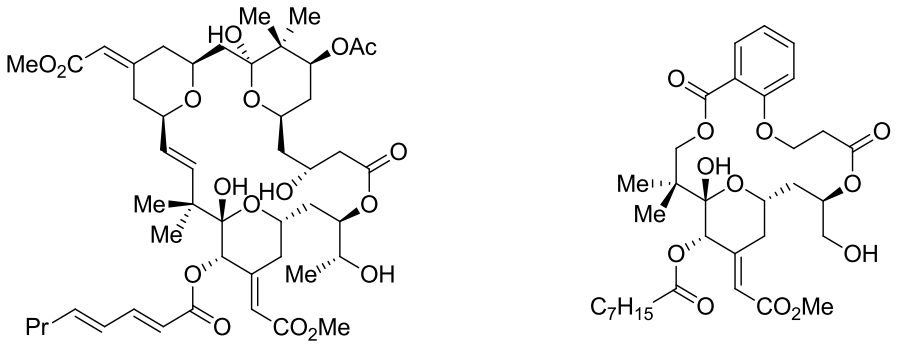


Figure 9. Bryostatin and its salicylate analogue developed through CAR studies

Halaven® (eribulin mesylate) is a potent antitumor agent that is a derivative of the structurally complex marine natural product halichondrin B (Figure 10).[141-146] It can be seen, that while Halaven® has a simplified polyether structure when compared to halichondrin B, it is still a highly complex molecule that is difficult to access in large quantities. However, due to the impressive biological activity observed when Halaven® was screened in clinical trials, a viable synthetic route to significant amounts of this compound was necessary. The Kishi group and Eisai Inc. embarked on this daunting undertaking, leading to a truly impressive synthetic route which allows for the synthesis of 200-300 g batches of the complex natural product derived Halaven®.[142-145, 147]

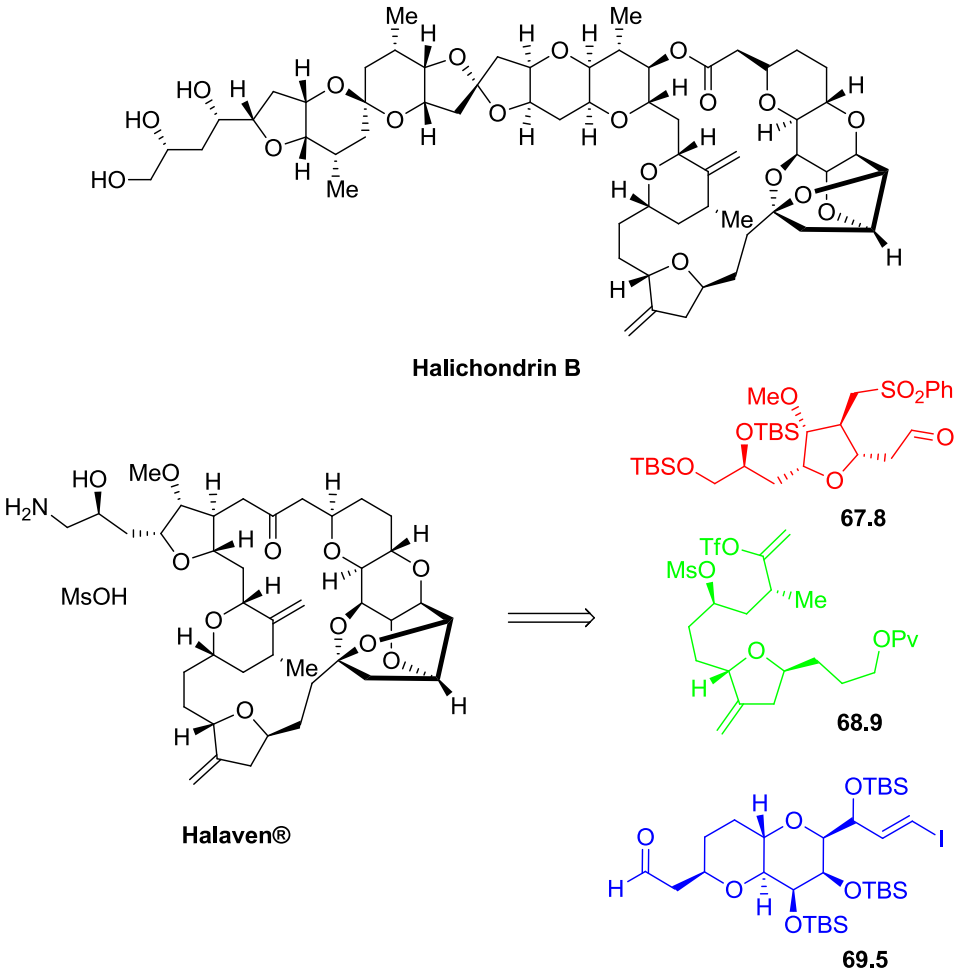
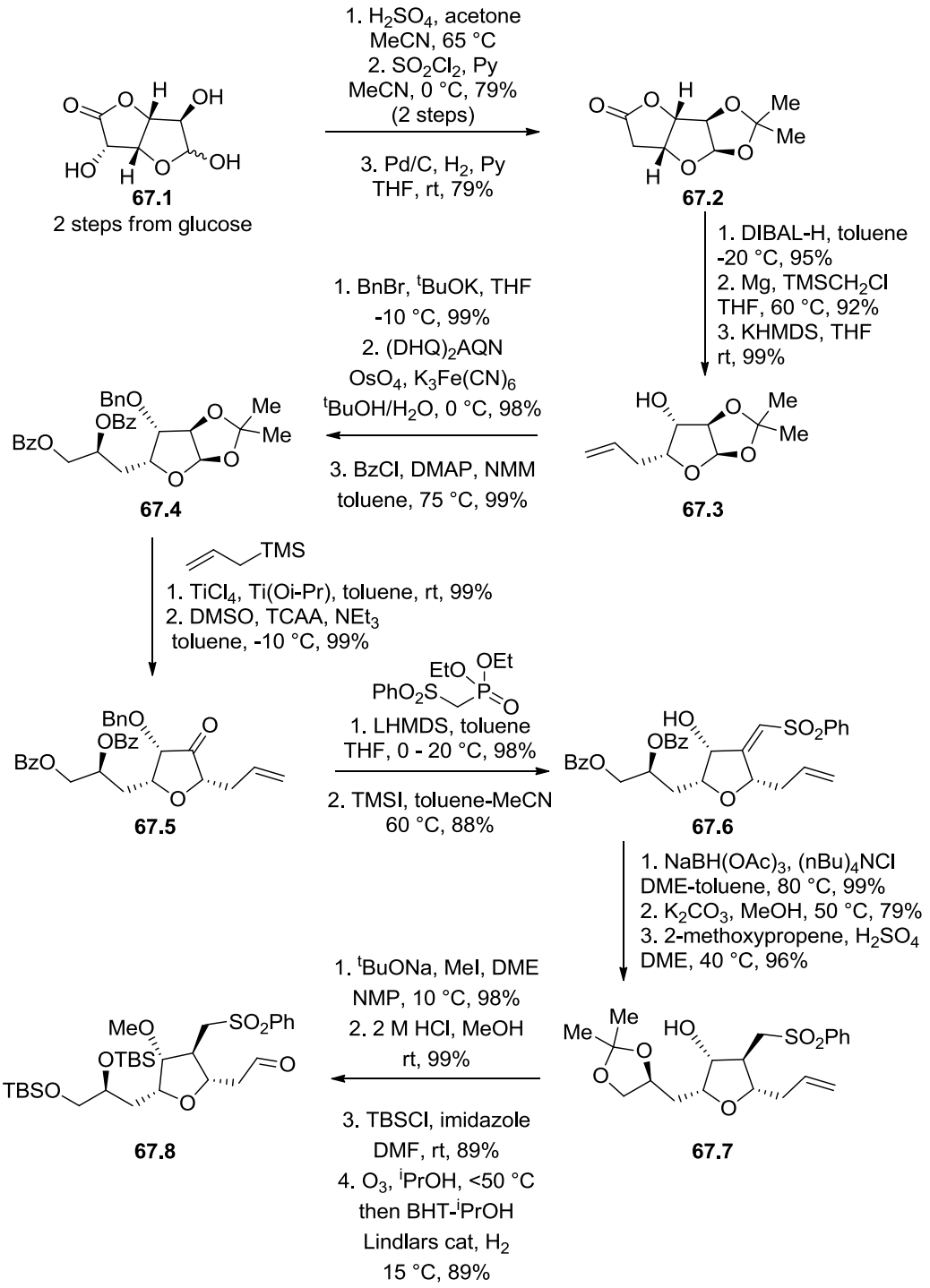


Figure 10. Halichondrin B and Halaven®

The synthesis of Halaven® proceeds through the generation of three key intermediates, aldehyde **67.8**, vinyl triflate **68.9** and vinyl iodide **69.5.** Synthesis of aldehyde **67.8** begins with the readily available D-glucurono-3,6-lactone **67.1**, involving ketal formation followed by α-chlorination and subsequent reductive dehalogenation to afford lactone **67.2** as a crystalline solid. DIBAL-H reduction of lactone **67.2** followed by addition of $TMSCH_2MgCl$ provides a β-hydroxysilane adduct which eliminates on treatment with KHMDS to afford alkene **67.3**. Protection of the alcohol group of alkene **67.3** with benzyl bromide and base afforded a benzylic ether, which underwent a Sharpless asymmetric dihydroxylation reaction, with the resultant diol group then protected as their benzoyl esters to afford pyran **67.4**. A titanium catalysed C-glycosidation reaction of pyran **67.4** using allyltrimethylsilane, was followed by modified Moffat oxidation (DMSO-trichloroacetic anhydride) of its secondary alcohol functionality to afford ketone **67.5**. Horner-Wadsworth-Emmons reaction of ketone **67.5** was then used to introduce a vinyl sulfone functionality followed by benzyl ether cleavage using iodomethylsilane to afford

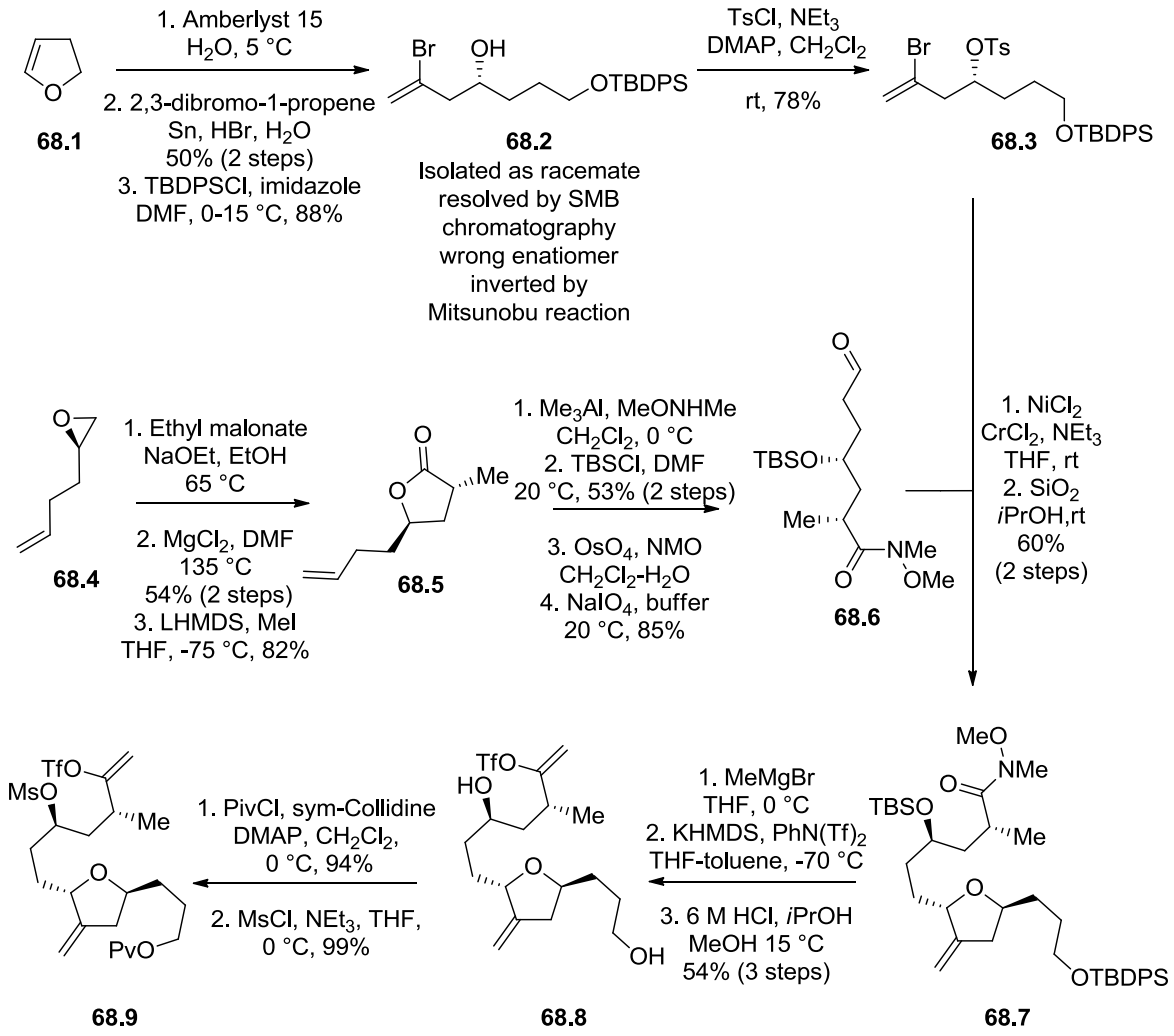
alcohol **67.6.** Hydroxyl-directed conjugate reduction reaction of the vinyl sulfone fragment of **67.6**, was followed by base mediated cleavage of both its benzoyl groups to afford a crystalline triol intermediate that could be purified to homogeneity. This triol intermediate was then re-protected to afford acetonide **67.7**. The alcohol functionality of **67.7** was then methylated, followed by a further protecting group swap to afford *vicinal* TBS ethers was then required to create protecting group uniformity later in the synthesis (*vide supra*). Ozonolysis of the terminal alkene using a reductive workup (Lindlars catalyst) then afforded crystalline aldehyde **67.8** (Scheme 67).[142, 145] While the use of a biorenewable sugar based starting material represents an admirable feature of this synthesis it should be noted that chiral sugars are highly functionalised substrates that often require multiple synthetic steps to remove redundant functionality.



Scheme 67. Synthesis of aldehyde **67.8**

The synthesis of triflate **68.9** began with acid catalysed hydration of dihydrofuran **68.1**, followed by a tin-mediated 2-bromoallylation reaction to afford a crystalline racemic diol, whose primary alcohol was selectively *O*-silyl protected to afford vinyl bromide **68.2**. The enantiomers of **68.2** were resolved through chiral-simulated moving bed (SMB) chromatography using

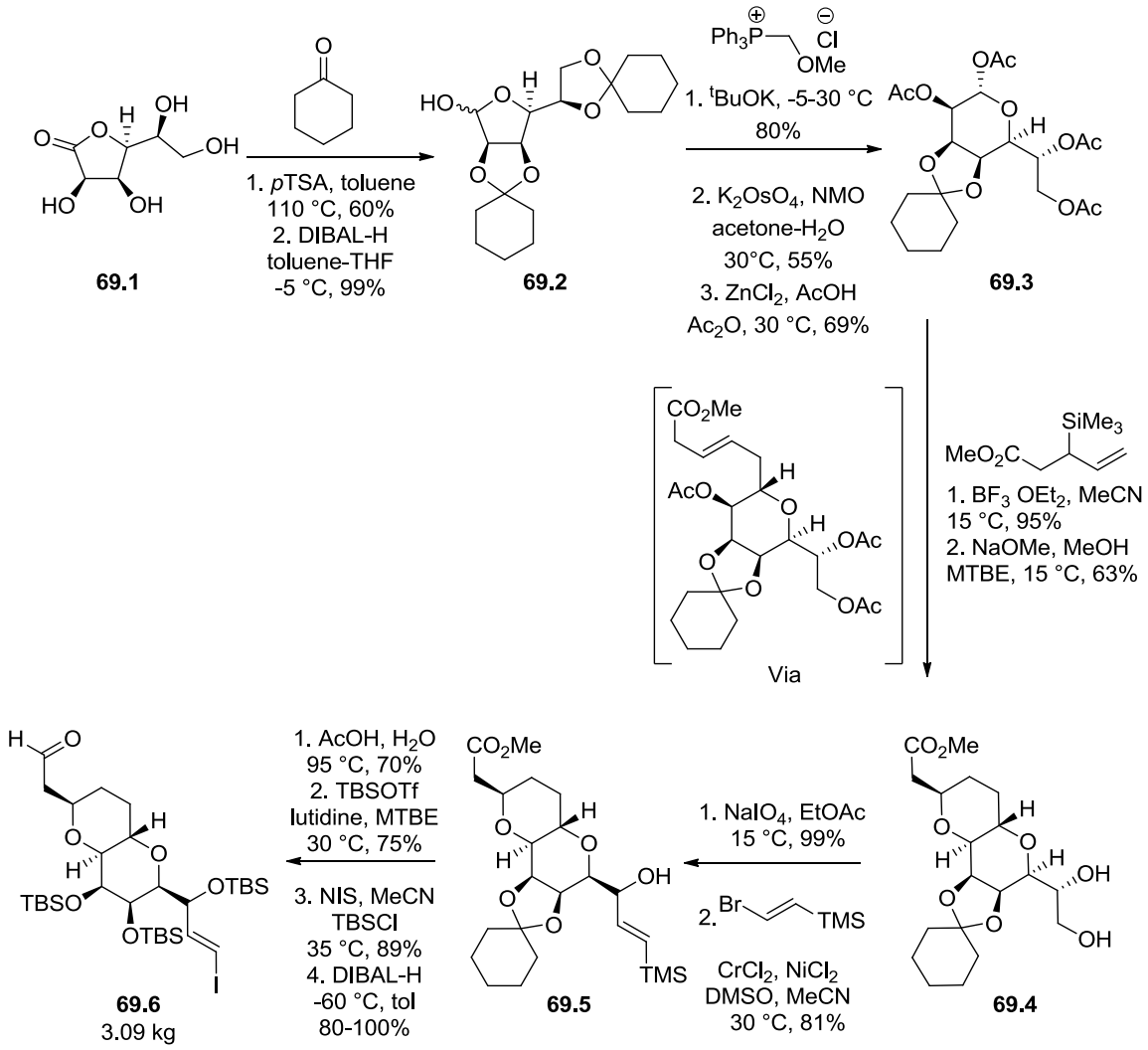
Chiralpak OD as a chiral stationary phase, affording the desired (*R*)-alcohol **68.2** in >98% ee. The unwanted (*S*)-enantiomer could then be inverted to the desired (*R*)-enantiomer through the use of Mitsunobu chemistry. Tosylation of alcohol **68.2** using tosyl chloride and DMAP afforded vinyl bromide **68.3**, that underwent a Nozaki–Hiyama–Kishi (NHK) Ni(II) catalysed cross-coupling reaction with Weinreb amide **68.6** (obtained in 7 steps from epoxide **68.4**), to afford a coupled allylic alcohol that was treated with SiO_2 in *iso*-propanol, resulting in cyclisation with loss of its tosyl group to generate the tetrahydrofuran ring of **68.7**. Grignard addition of MeMgBr to Weinreb amide **68.7** generated a ketone, which when treated with KHMDS and phenyl triflimide gave its kinetic enol triflate that was *O*-silyl deprotected to give alcohol **68.8**. Subsequent *O*-pivaloyl and *O*-mesyl protections led to the synthesis of vinyl triflate **68.9** in 2.1% yield over a total of 15 steps (Scheme 68).[145]



Scheme 68. Synthesis of triflate **68.9**

Synthesis of aldehyde **69.6** began with acid catalysed bis-diol protection of D-gluconolactone **69.1** with cyclohexanone to afford a bis-cyclohexylidene lactone, with subsequent DIBAL-H reduction of its lactone functionality generating lactol **69.2**. A series of transformations including Wittig reaction of $MeOCH_2PPh_3^+Cl^-$, dihydroxylation reaction of the resultant alkene, and bis-acetylation led to the formation of bis-acetate **69.3**. A key Lewis acid catalysed C-glycosidation reaction of bis-acetate **69.3** was carried out with 3-trimethylsilyl-4-pentenoate to give the important fused pyran functionality of ester **69.4**. Periodate mediated cleavage of the diol fragment of **69.4** was followed by subsequent NHK reaction of the resultant aldehyde with 1-bromo-2-trimethylsilylethene afforded allylic alcohol **69.5**. A protecting group swap from cyclohexylidene to *tert*-butyldimethylsilyl ether groups, was then followed by

conversion of the vinyl-silane fragment into a vinyl-iodide group to generate >3 Kg of vinyl iodide **69.6** (Scheme 69).[146]



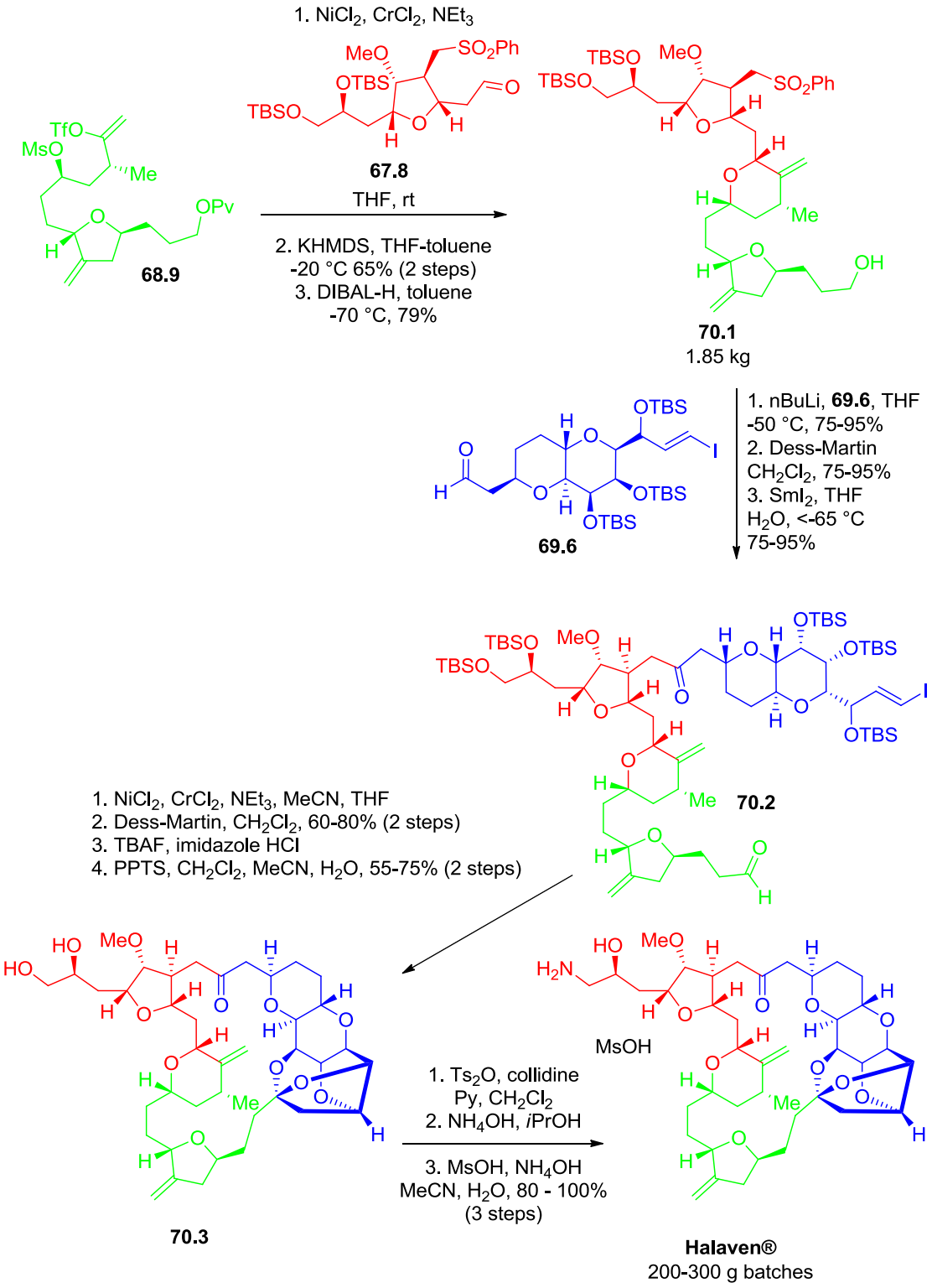
Scheme 69. *Synthesis of aldehyde **69.5***

Aldehyde **67.8** and vinyl triflate **68.9** (prepared in 15 steps) were then combined utilising a third NHK Ni(II) catalysed cross-coupling reaction, with subsequent cyclic etherification to afford the pyran ring being achieved through titration with KHMDS, which resulted in intramolecular mesylate displacement by its δ-alkoxide substituent. Reductive cleavage of the pivolate with DIBAL-H then afforded alcohol **70.1**, which was prepared on a 1.85 kg scale. Coupling of of the sulfonyl anion of alcohol **70.1** with the aldehyde functionality of vinyl iodide **69.6** (prepared on a 3.04 kg scale in 12 steps), was followed by alcohol oxidation and samarium

iodide mediated reduction of the sulphonyl group to afford ketone **70.2**. An intramolecular NHK reaction and subsequent alcohol oxidation was then followed by global *O*-Silyl deprotection and intramolecular ketalization reactions to afford diol **70.3**. Introduction of the amine functionality was then achieved by tosylation of the primary alcohol, allowing for *in situ* epoxide formation. Epoxide opening with ammonium hydroxide, and generation of a stable mesylate salt afforded Halaven® in 200-300 g batches (Scheme 70).[142, 145, 147]

A highly convergent approach combined with a strategy for targeting crystalline intermediates, were key factors in bringing this incredible syntheses to fruition, and ultimately generating usable quantities of Halaven® to allow for biological testing in the clinic. These trials proved successful and Halaven® is currently used as a cancer therapy drug for patients suffering with advanced breast cancers and inoperable liposarcoma. However, the National Institute for Clinical Excellence (NICE) originally rejected its availability on the NHS, with its cost of >£10,000 for a 6 month treatment programme for only an average 3 month life expectancy extension deemed too costly. However, public pressure eventually forced NICE to reverse their decision and this drug is now available in the UK.

This synthesis is of course an incredible achievement of organic chemistry, however, as mentioned above there are a number of protection/deprotection steps and inherently inefficient protecting group swaps. This results in an additional 17 synthetic steps, and as the art of organic synthesis evolves, it is hoped that these kind of wasteful, but currently necessary, protecting group processes may ultimately be removed completely.



Scheme 70. Synthesis of Halaven®

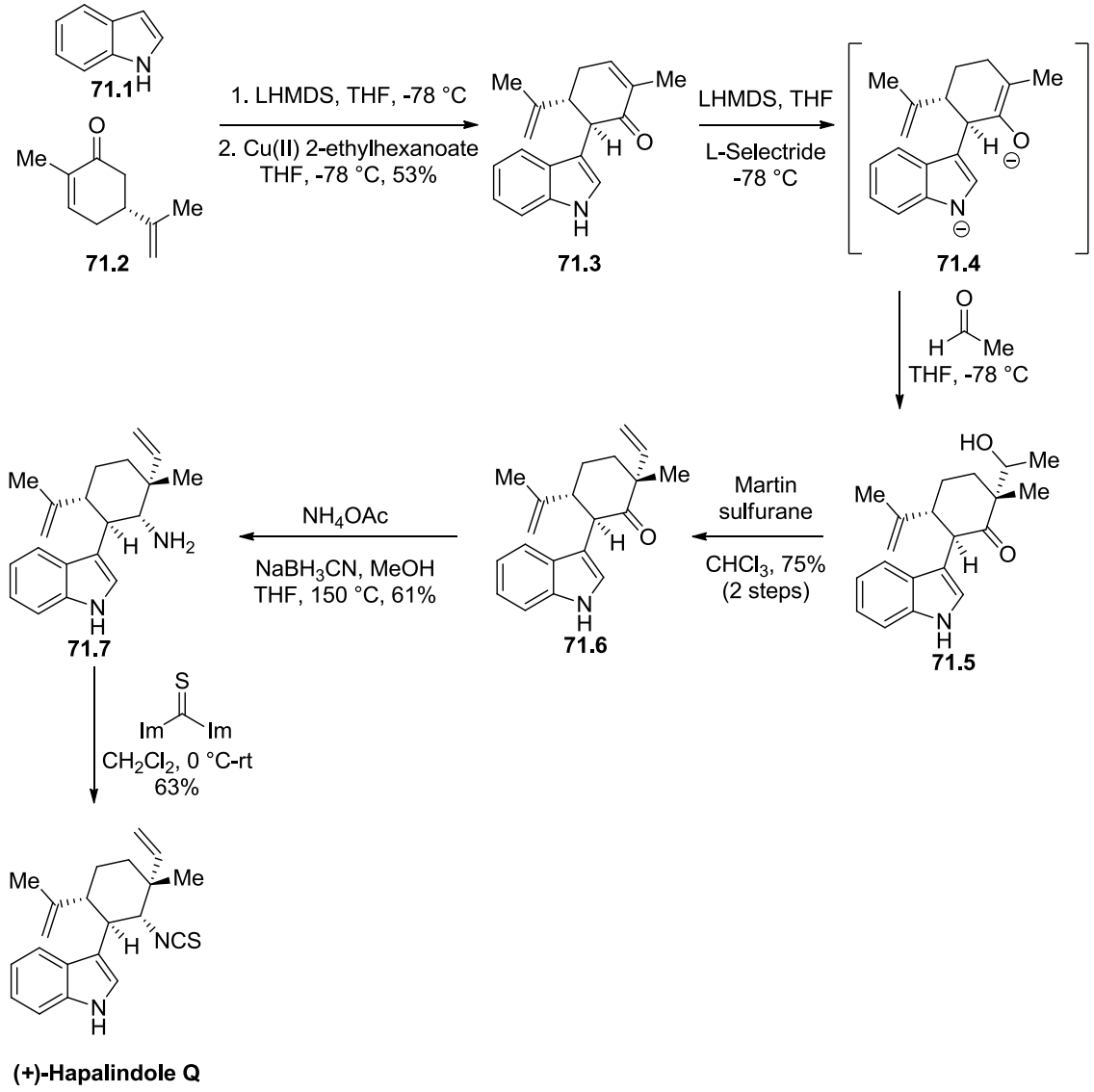
The emergence of divergent total synthesis and the recent decrease in new pharmaceutical leads based on natural products, potentially highlights some of the perceived shortcomings of natural product synthesis. It has long been argued that semi-synthesis is the only way to produce sufficiently large enough amounts of naturally occurring materials for drug-discovery applications. However, it must be accepted that this promise is rarely met.[98] Therefore, it can be argued that natural product synthesis in the 21st century should always seek to provide the target compound in multigram quantities, with synthesis on this scale presenting many challenges associated with logistics, the sustainable use of reagent and disposal of side products and waste.[147] In this respect the defined principles and metrics of green and sustainable chemistry are likely to be increasingly used as a tool to devise efficient syntheses that meet these demands.[148-153]

4.0 Protecting Group Free Synthesis

As mentioned earlier the use of protecting groups are common place in many complex synthetic routes towards natural products. However, their use is acknowledged as a necessary evil, "*synthetic chemists would dearly like to be able to work without protecting groups, but they are very glad that they exist"* (P. Kocienski).[154] The disadvantages associated with the use of protecting groups are obvious, an increase in the number of synthetic steps, a reduction in overall yield, and an increase in the amount of waste produced. However, the reason that their use is so prolific is because of the inherent security and predictability that they confer, allowing for increased functional group compatibility that allows for a vast increase in the completion rate of structurally complex targets.[128, 129] Therefore, organic synthesis faces an enormous challenge in trying to change this reliance and move towards more efficient protecting group free synthetic protocols. However, this can also be seen as a *"opportunity for invention"*.[128] New reactions, regents and catalysts will need to be developed with a focus on chemoselectivity and functional group compatibility if this challenge is to be met. While this is clearly a daunting task there are a number of research groups that are embracing this challenge, resulting in the number of reported protecting group free syntheses of natural products increasing significantly over the past decade or more.[128, 129, 155]

An impressive early landmark example of a protecting group free synthesis, where protecting groups were deliberately avoided through synthetic design, rather than being found to be unnecessary, was the synthesis of (+)-hapalindole Q by Baran and Richter in 2004 (Scheme 71).[155]

Their synthesis began by inventing a new reaction to couple together the naturally available starting materials indole **71.1** and carvone **71.2**. Deprotonation of both reagents, gave the aza-anion of indole and the enolate of carvone, which were subjected to copper mediated oxidation to afford their corresponding radicals that underwent radical coupling to give the 3-substituted indole **71.3**. Deprotonation of indole followed by conjugate reduction of the resultant aza-anion with L-selectride, afforded an enolate intermediate **71.4**, treatment with acetaldehyde gave aldol **71.5**. The secondary alcohol functionality of **71.5** was then dehydrated using Martin's Sulfurane to give bis-alkene **71.6**. Reductive amination of the ketone functionality of **71.6** resulted in primary amine **71.7** which was converted into its corresponding isothiocyanate *via* treatment with thiocarbonyldiimidazole to give the final compound (*+*)-hapalindole Q.[155] This synthesis is not only a great example of protecting group free natural product synthesis, but also an example where natural product synthesis served as a driving force for the development of a new indole coupling reaction.[128, 155]



Scheme 71. Protecting group free synthesis of hapalindole Q[155]

Since this outstanding demonstration of protecting group free synthesis, interest in this area has increased steadily, resulting in the publication of some exciting and inspiring natural product syntheses.[128, 129, 156-166] This report will now focus on a few recent examples of protecting group free natural product synthesis, starting with a discussion of a formal synthesis of (-)-platencin (Figure 11).

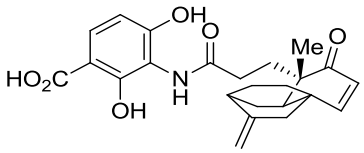
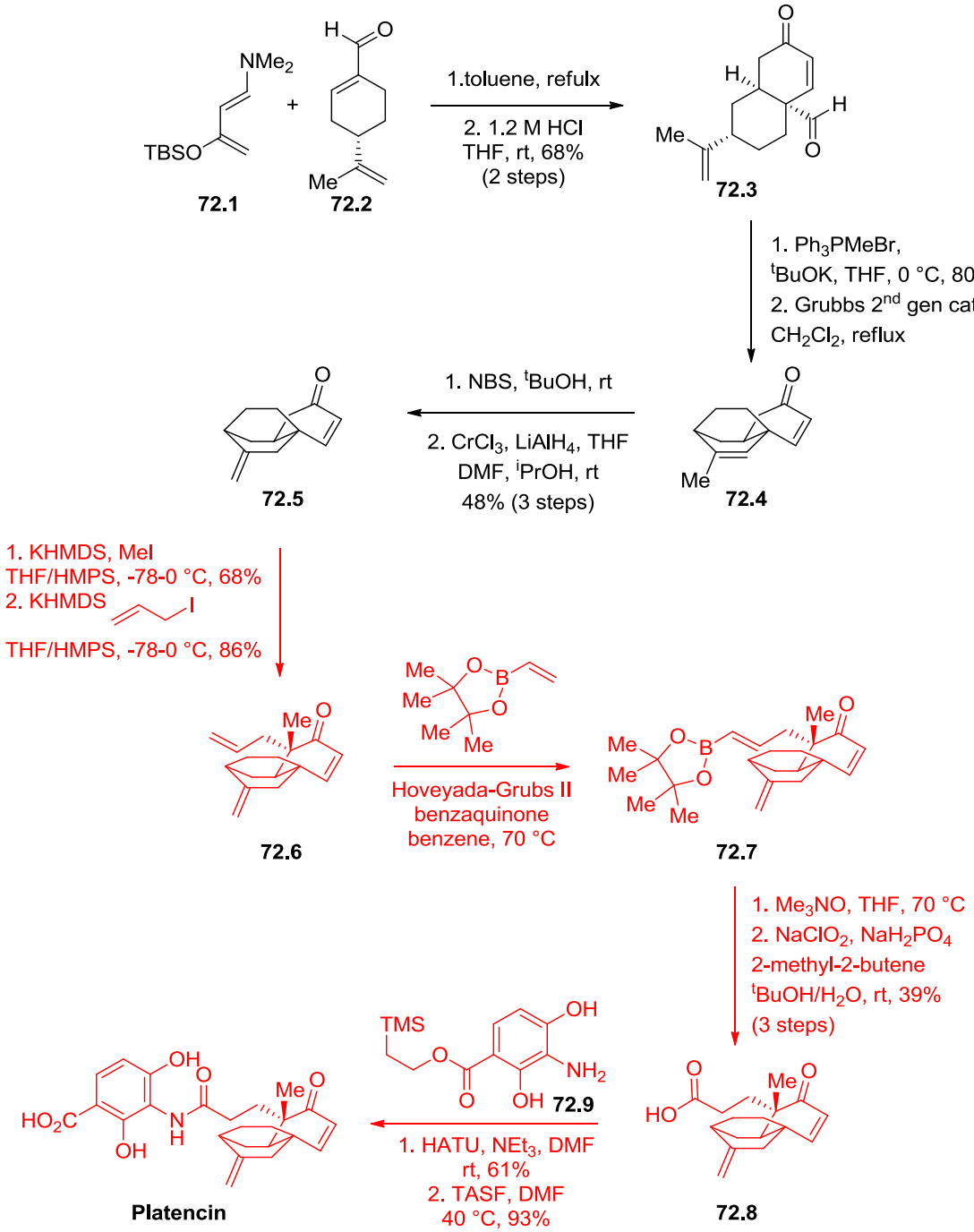


Figure 11. (-)-Platencin

(-)-Platencin is a potent, broad spectrum Gram-positive antibiotic.[167] The first total synthesis by Nicolaou *et al.*[167] in 2008 followed a traditional protecting group strategy in 23 steps, however, this publication was quickly followed by an efficient "protecting group free" formal synthesis by Tiefenbacher and Mulzer affording platencin in 13 steps from perillaldehyde (Scheme 72).[168]

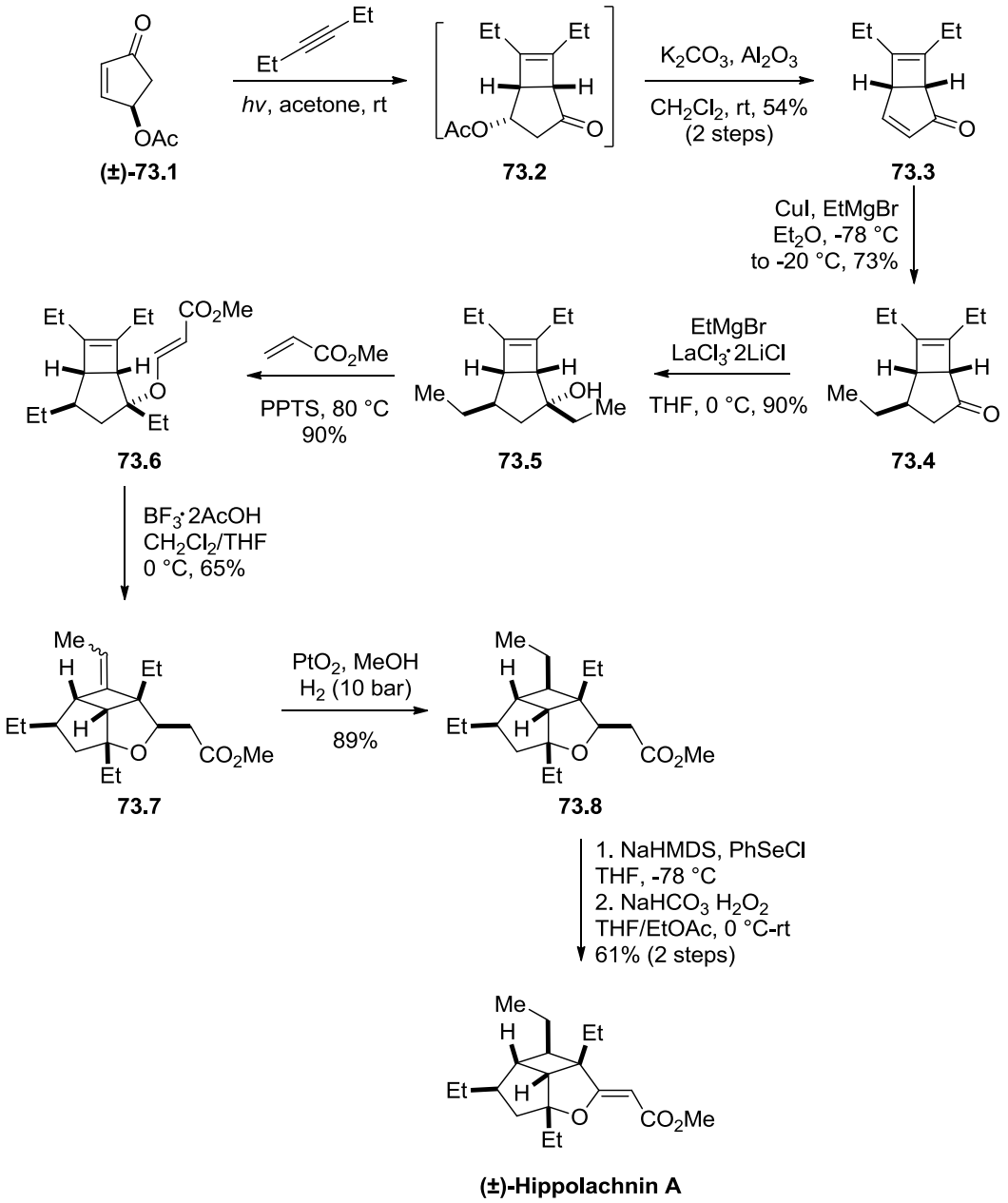
Their formal synthesis began with a Diels-Alder cyclisation of Rawal diene **72.1** and (-)-perillaldehyde **72.2** to give α,β-unsaturated ketone **72.3**. A selective Wittig reaction of the aldehyde group was then performed to give a bis-terminal alkene which upon treatment with Grubbs 2nd generation catalyst, resulted in a ring closing metathesis reaction to afford fused tricycle **72.4**. Alkene bond migration was performed *via* bromoalkene formation with NBS, which upon treatment with $CrCl_3$ and $LiAlH_4$ gave the desired tricycle **72.5**, containing an exocyclic alkene bond which was a common intermediate in both syntheses (Scheme 72).[167, 168] The remaining synthetic steps (shown in red) show the completion of the synthesis according Nicolaou's methodology.[167] Sequential enolate alkylation with methyl iodide and allyl iodide afforded triene **72.6**, which underwent regioselective cross-metathesis with vinyl boronate using a 2nd generation Hoveyda–Grubbs catalyst and benzoquinone to afford boronate **72.7**. Boronate oxidation (using Me_3NO), followed by Pinnick oxidation of the resultant alcohol afforded carboxylic acid **72.8**. This acid then underwent an amide bond coupling reaction with aniline **72.9**, using a HATU facilitated coupling agent, followed by acid deprotection to afford *(-)*-Platencin (Scheme 72).[167]



Scheme 72. Formal synthesis towards the synthesis of (-)-platencin[168]

(±)-Hippolachnin A is a recently isolated marine polyketide, possessing an intriguing fused molecular framework that displays promising antifungal activity.[157] The first total synthesis of (±)-hippolachnin A was completed in 2015 by the Carreira group, who described a protecting group free synthesis of (±)-hippolachnin A in nine linear steps and an overall yield of 9%. The synthesis began with commercially available cyclopentenone **73.1** which was irradiated with

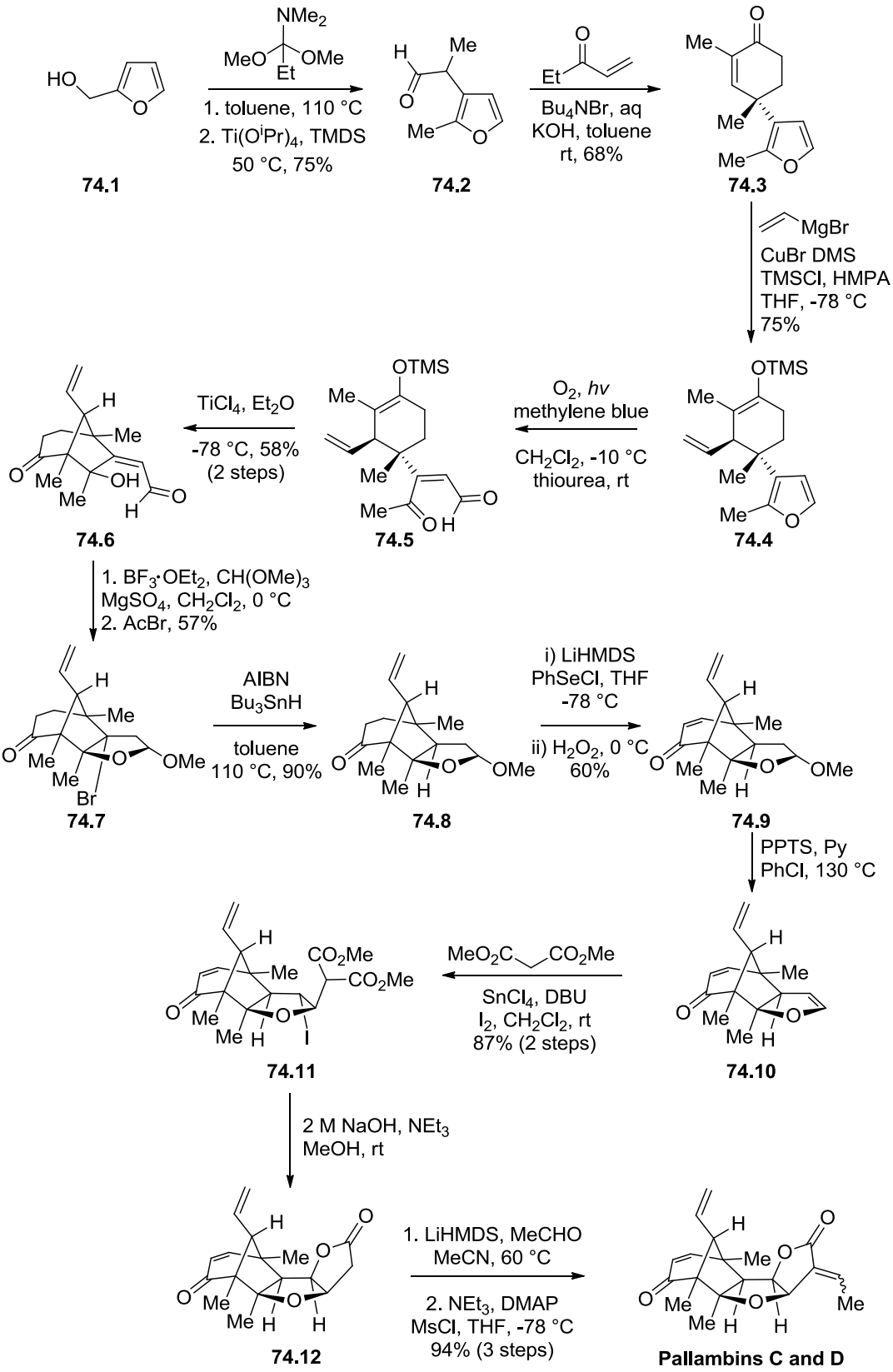
hex-3-yne at λ>270 nm, undergoing a [2+2] photocycloaddition reaction to afford bicyclo[4.2.0]heptanone **73.2**. This photoadduct was found to be susceptible to elimination during purification, therefore it was reacted directly with K_2CO_3 to generate enone **73.3**. 1,4-cuprate addition of an ethyl fragment, followed by 1,2-Grignard addition of a second ethyl fragment afforded alcohol **73.5** with complete *exo* diastereoselectivity. Treatment of alcohol **73.5** with methyl acrylate in the presence of pyridinium *para*-toluenesulfonate (PPTS) then gave ester **73.6** as a cyclisation precursor. Reaction of ester **73.6** with BF_3·2AcOH resulted in an ene cyclization reaction occurring to give the desired tricyclic annulated product **73.7** in a 6:1 diastereomeric ratio. Heterogeneous platinum catalysed hydrogenation of **73.7** then gave the *exo* product **73.8**. The synthesis of (±)-hippolachnin A was completed by α-phenylselenylation of the enolate of the ester functionality of **73.8**, followed by oxidation of the crude reaction mixture with concomitant selenoxide elimination to afford the desired alkene (Scheme 73).[157]



Scheme 73. Synthesis of Hippolachnin A

The pallambins are terpene natural products, that whilst exhibiting no known bioactivity, possess a fascinating structural architecture, containing 4-6 rings and 7-10 contiguous stereocentres.[156] A recent report by the Baran group has demonstrated a highly strategic and protecting group free synthesis of pallambins C and D, with their syntheses having been intentionally designed to eliminate extraneous redox operations and functional group interconversions.

The synthesis began with the abundant feed stock chemical furfuyl alcohol **74.1** which is sourced from furfural that is a major biorewable feedstock obtained from sugar cane bagasse. Tandem Eschenmoser-Claisen rearrangement and reduction of the resultant amide was carried out in a one-pot reaction to afford aldehyde **74.2** (a significant improvement on the previous synthesis of aldehyde **74.2**). A Robinson annulation of aldehyde **74.2** with ethyl vinyl ketone was then used to generate cyclohexenone **74.3**. 1,4-Vinyl cuprate addition of **74.3**, was followed by work-up with TMSCl to afford the activated TMS-enol ether **74.4**. Photosensitised chemoselective oxidative cleavage of the furan heterocycle resulted in keto-aldehdye **74.5** which was used in its crude form in the next step, as decomposition occurred during attempted purification. A titanium catalysed Mukaiyama aldol cyclisation of the TMS-enol ether fragment of **74.5** onto its ketone fragment generated the pivotal bicyclo[3.2.1]octane skeleton of **74.6**. It is believed that the reaction proceeds via reaction at the less electrophilic methyl ketone group due to geometric constraints preventing the enol ether engaging with the aldehyde group. Intramolecular BF_3 catalysed acetal formation led to the spontaneous generation of the pyran ring to afford a mixed acetal, which on treatment with AcBr furnished bromide **74.7**. Halogen removal *via* treatment with AIBN/Bu_3SnH then afforded alkene **74.8**. Treatment of **74.8** with LiHMDS and PhSeCl, followed by oxidation, afforded a selenoxide that underwent spontaneous elimination to afford α,β-unsaturated ketone **74.9.** Subsequent acid catalysed methanol elimination then afforded the sensitive, but thermally stable dihydrofuran **74.10**. A new enol-ether difunctionalisation reaction, involving reaction of the tin-enolate of dimethyl malonate with dihydrofuran **74.10**, followed by addition of I_2 afforded the desired iodo-diester **74.11**. The final cyclisation sequence to generate the desired fused tetracycle was performed utilising a one pot sequence: (i) alkaline hydrolysis of the esters (2 M NaOH); (ii) Et_3N-induced lactonisation and decarboxylation; (iii) aldol addition to acetaldehyde, and (iv) elimination of the β-hydroxyl group using MsCl/NEt_3 to give the desired pallambin C (Z alkene) and pallambin D (E alkene) in a 1:2 ratio (Scheme 74). This impressive synthesis was completed in just 16 steps (11 one pot reactions), with only two steps not being involved in forming bonds present in the final natural products. While this is an elegant and efficient synthesis, it does however, utilise some undesirable reaction conditions. In particular the tin based reagents (Bu_3SnH, $SnCl_4$) are highly toxic and should be avoided wherever possible, while the use of phenylselenyl chloride is also highly toxic, leads to generation of stoichiometric amounts of toxic waste.



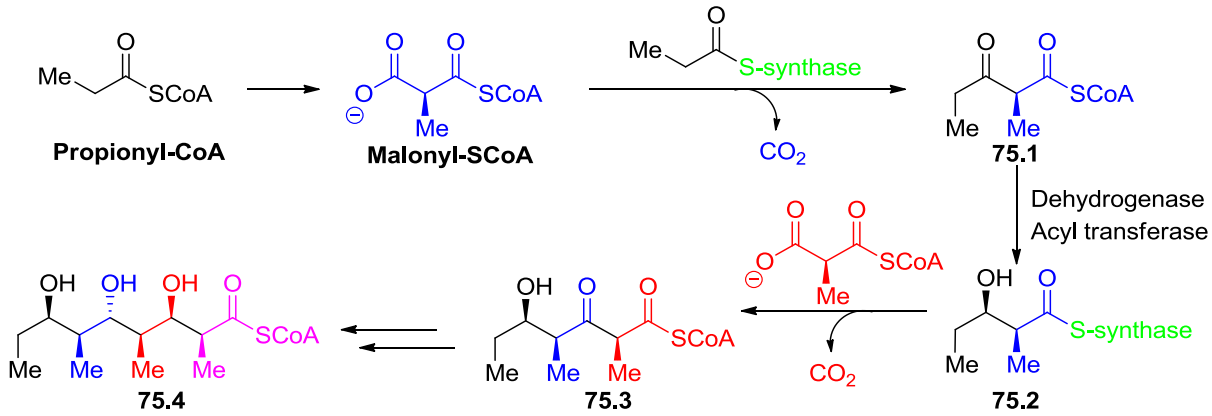
Scheme 74. Synthesis of Pallambins C and D

In conclusion, although protecting group free syntheses often require reaction ingenuity, invention and significant reaction optimisation, the end results more than justify the effort required, due to the significant reduction in the number of steps required, the improvement in atom economy and the reduction in the number of redox steps required.[128, 129] However, while there are many elegant protecting group free publications emerging, it should be noted that the vast majority of these natural product syntheses do not contain multiple free hydroxyl groups, or other functional groups that have highly acidic protons. This clearly highlights an area of natural product synthesis where there is still room for further development.

5.0 Polyketides

5.1 Introduction to Polyketides

Polyketides are an enormous class of natural products synthesised by a wide range of organisms; bacteria, fungi and plants.[169, 170] They are biosynthesised through a series of polycondensation reactions using simple carboxylic acid donors in the form of their corresponding thioesters; acetyl-SCoA, propionyl-SCoA and malonyl-SCoA. These polycondensation reactions are performed by a range of polyketide synthases (PKS) to form a series of acyclic or cyclic molecules, containing contiguous stereocentres, with a simplified representation of their biosynthesis shown below (Scheme 75).[169-171]



Scheme 75. *Biosynthetic pathway to polyketides*

In order to further exemplify this complex process, a ‘cartoon’ version of the erythromycin PKS assembly line is shown in Figure 12, in which circles depict enzymatic domains whose linker regions have been omitted for clarity. From this figure it can be seen that each of the DEBS (6-deoxyerythronolide B synthase) proteins contains two functional units or modules. Each module contains the three domains required to catalyse one cycle of chain extension (ketosynthase (KS), acyltransferase (AT) and acyl carrier protein (ACP)) as well as a variable set of domains (ketoreductase (KR), dehydratase (DH) and enoyl reductase (ER)) associated with functional group modification. Throughout the entire biosynthetic sequence, the polyketide chains remain bound to the PKS. The three essential domains KS, AT and ACP, co-operate to catalyse carbon–carbon bond formation by Claisen condensation, which results in a β-keto ester intermediate. The variable set of domains positioned between the AT and ACP (depicted as a loop above the line of essential domains) carry out reductive modification of the keto group before the next round of chain extension.

Once the acyclic polyketides are synthesised, further enzymatic transformations can be performed to produce a bewildering array of natural products, including those containing cyclic, acyclic, small, large, simple, aromatic, and highly complex structures (Figure 12 and Figure 13).[169, 171]

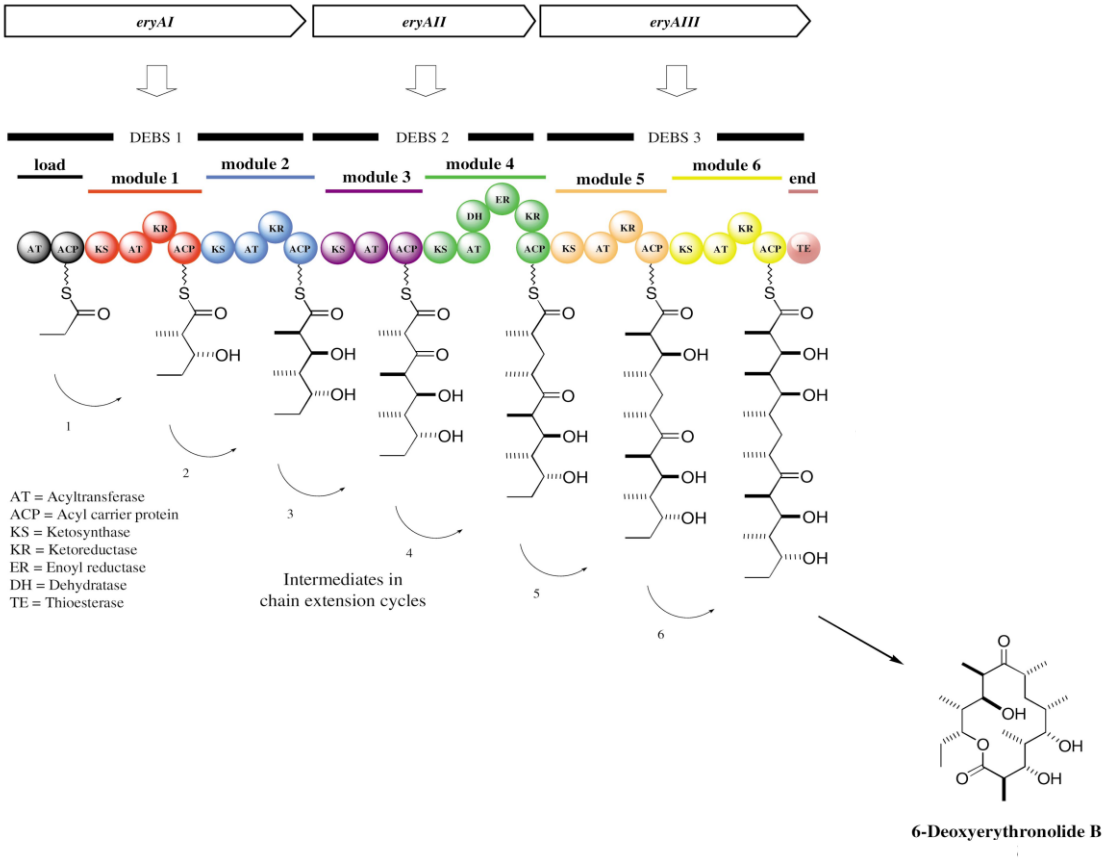


Figure 12. Domain organisation of the erythromycin polyketide synthase[171]

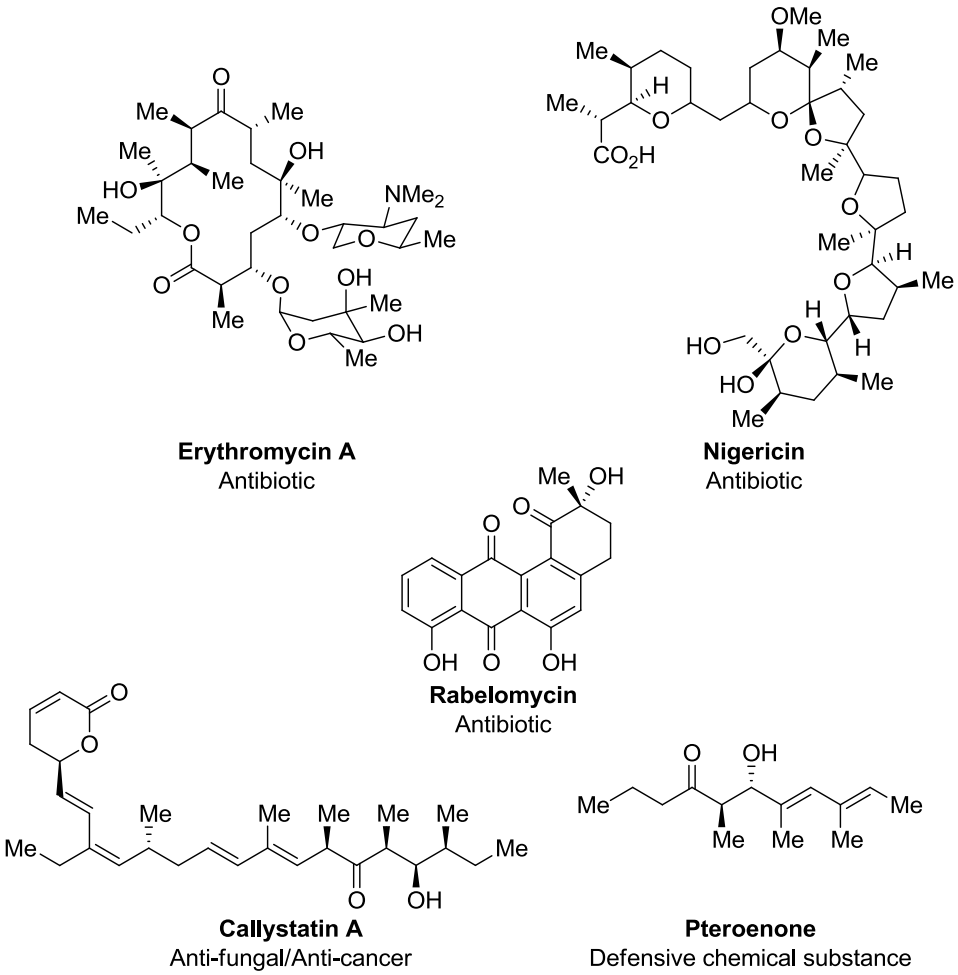


Figure 13. Examples of naturally occurring polyketides[169]

Due to the large variety in thier structure, polyketides exhibit a wide range of biological activities including; antibiotic, cancer chemotherapeutic, antifungal and cholesterol lowering agents.[169] There are around 10000 known polyketide structure, however, this number is ever increasing with new natural product sources being discovered almost daily. Of these compounds about 1% have been shown to possess useful drug activity, which is about five times higher than the average normally found for natural products. This highlights that polyketides are a potentially excellent source of lead compounds for the discovery of future drug molecules.[169, 172]

Polyketides can be grouped into three smaller subclasses; fatty acids, polypropionates and aromatic polyketides.[169] Although these groups are structurally diverse, there are several structural features which are common among many polyketides, including the stereotetrad motif shown in Figure 14.

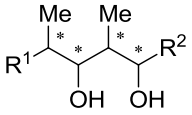


Figure 14. General structure of a stereotetrad

The presence of four contiguous stereogenic centres gives rise to the possibility of eight stereoisomeric combinations occurring as fragments within the structure of a polyketide natural products (Figure 15). Indeed, all of these tetrad combinations are known to be present in polyketide natural products.[169]

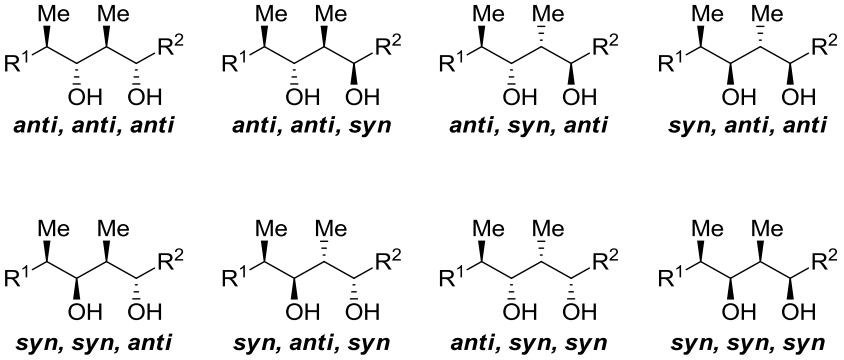
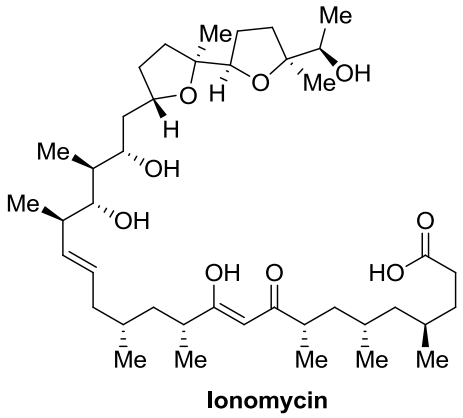


Figure 15. Possible diastereomeric combinations of the stereotetrad

Although, polyketides containing these stereotetrad fragments are abundant in nature, their stereoselective synthesis still represents a formidable challenge to chemists, who have developed an armamentarium of synthetic strategies that they currently employ for their preparation. Consequently, the following section briefly reviews methodology that has been employed for the synthesis of representative polyketide natural products.

5.2 Synthesis of Ionomycin

Ionomycin (Figure 16) is a polyether antibiotic containing an *anti, anti, anti* stereotetrad which was first isolated in 1978 from the fermentation broths of *Steptomyces congoblatus.*[173, 174] Ionomycin is able to chelate to inorganic cations, with a particular affinity for calcium. This allows ionomycin to act as an ionophore to transfer cations across cell membranes,[169, 175, 176] which has made it an important molecule in neurochemical research.[169]



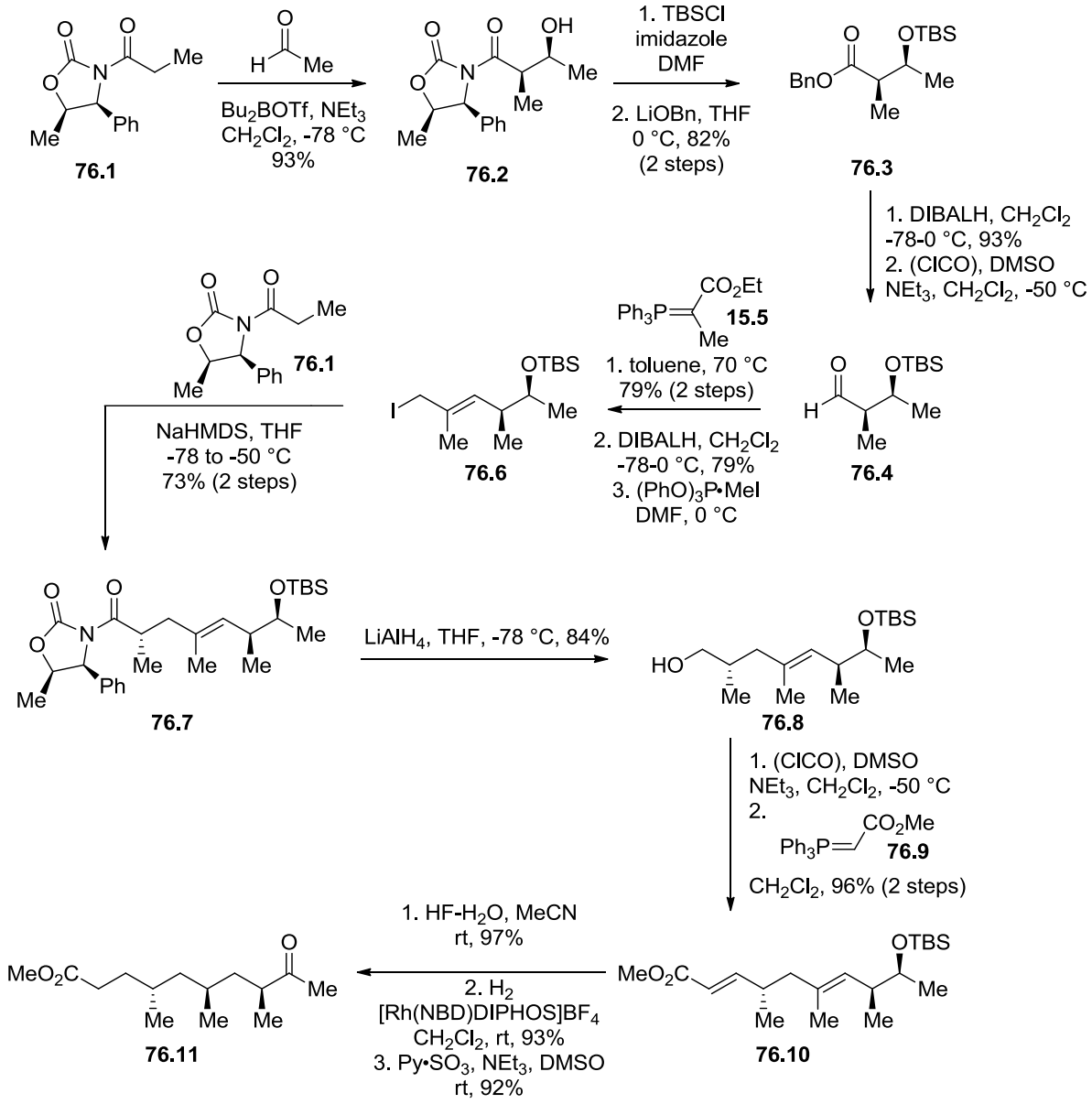
Ionomycin

Figure 16. Structure of ionomycin

There have been a number of total syntheses of ionomycin starting in 1990 by the Evans group[177] which based their synthesis on the use of chiral auxiliaries to achieve stereocontrol. The Evans auxiliary methodology utilises an iterative approach to build up vicinal stereocentres, whereby small fragments are gradually lengthened and functionalised through addition and removal of chiral auxiliaries to confer stereocontrol to aldol/alkylation reactions. This methodology allows for high levels of stereocontrol of these aldol reactions, and as such has become one of the most widely used methods for the synthesis of highly complex acyclic polyketides. However, it must be recognised that it is inherently wasteful due to the use of multiple stoichiometric auxiliary steps. Which cause extra steps introducing and removing the chiral auxiliary fragment (Scheme 76).

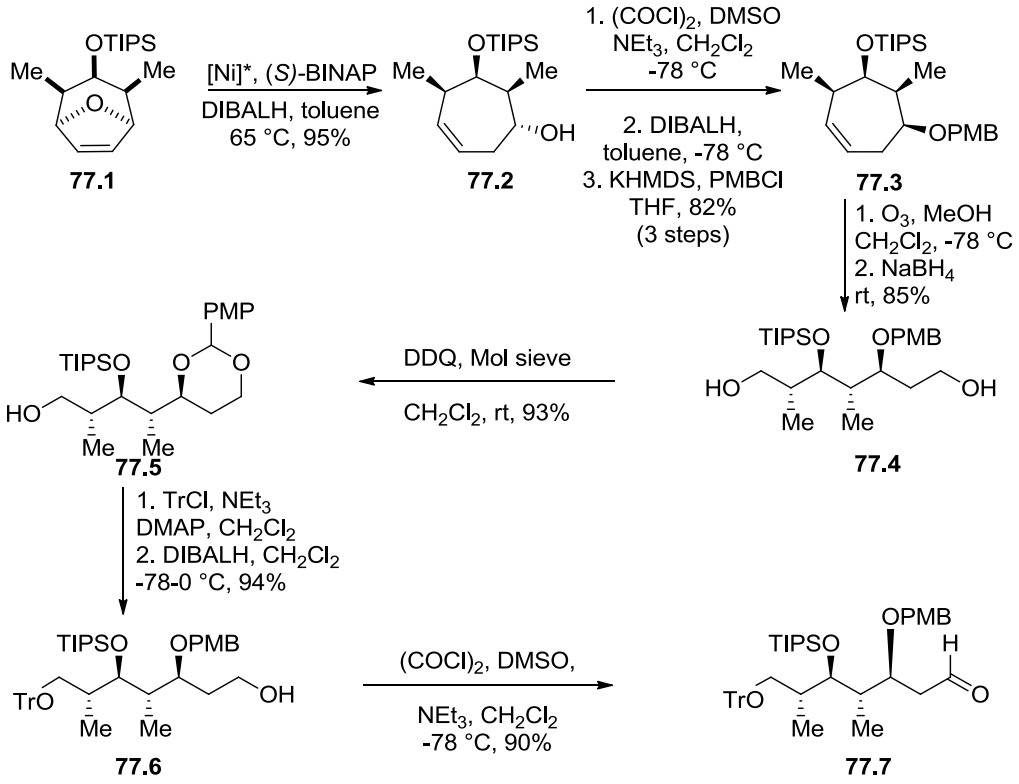
The synthesis of key fragment **76.11** that was employed for the synthesis of ionomycin can be used to illustrate this. The boron enolate of norephedrine-based auxiliary **76.1** was reacted with acetaldehyde to afford aldol adduct **76.2** in 93% yield and >98% de. The secondary alcohol was then *O*-silyl protected prior to auxiliary removal, *via* treatment with LiOBn to afford benzyl ester **76.3**. The ester functionality was then reduced to the primary alcohol and subsequently re-oxidised to the aldehyde **76.4**. Wittig olefination of **76.4** with ylide **76.5**, followed by ester reduction and subsequent iodination gave alkyl iodide **76.6**. Alkylation of the sodium enolate of *N*-propionyl-oxazolidin-2one **76.1** afforded carboximide **76.7**, the auxiliary fragment of which was then reduced to give primary alcohol **76.8**. A Swern oxidation and Wittig olefination with ylide **76.9** then afforded diene **76.10**. Silyl ether cleavage with $HF_{(aq)}$, was then followed by a stereoselective rhodium catalysed hydrogenation reaction to reduce the alkene

functionality, with a final alcohol oxidation step then affording the key C_1-C_{10} fragment **76.11** (Scheme 76). This part of the synthesis if a good example of how Evans auxiliaries are deployed in natural product synthesis. While they offer excellent diastereoselctive control, their inclusion and removal considerably lengthens the synthesis. Furthermore, there are normally a number of redox manipulations (5 in a 15 step synthesis), including the global reduction of an ester followed by re-oxidation back to the aldehyde. While this approach can keep the yield high it is an incredibly wasteful method.



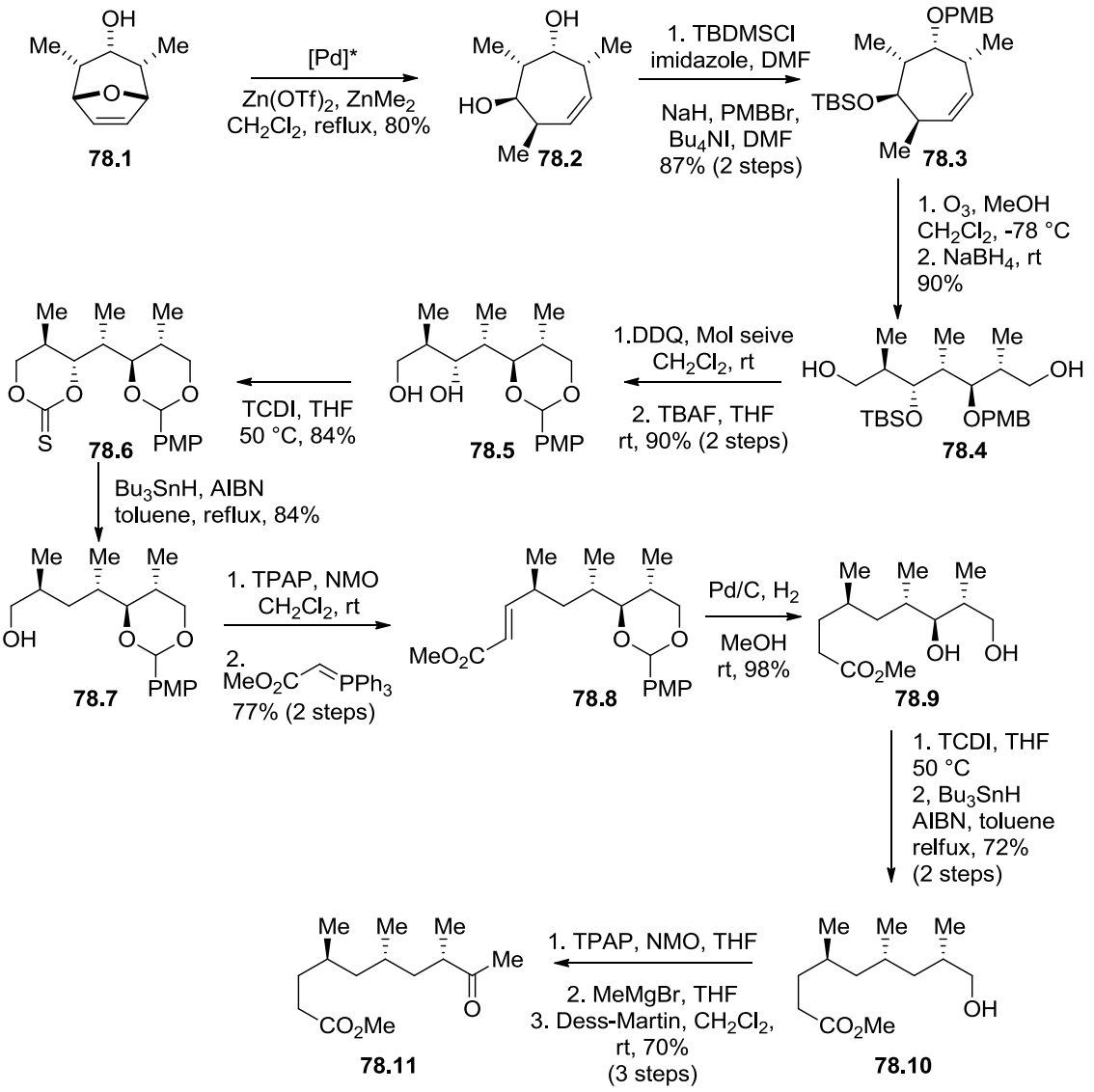
Scheme 76. Evans auxiliary methodology used for the synthesis of a key fragment **76.11** used for the synthesis of ionomycin

A more recent synthesis by Lautens *et al.* in 2002[175] based their stereotetrad methodology on ring opening strategies which are shown below in Scheme 77-Scheme 80. Their synthesis began with the symmetric oxabicyclic-[3.2.1]-alkenes **77.1** and **78.1** whose synthesis had previously been developed within their group, with each bicycle being used to synthesise separate fragments of the final compound. Oxabicyclic-[3.2.1]-alkene **77.1** was treated with a chiral nickel BINAP system to reductively desymmetrise the oxabicyclic ring to give alkene **77.2** in excellent yield (95%) and 93-95% ee. The alcohol stereocentre was then inverted *via* a 2-step oxidation/reduction protocol, followed by *O*-PMB protection to afford the protected diol **77.3**. Cleavage of the alkene *via* ozonolysis, followed by aldehyde reduction afforded acyclic diol **77.4**. Oxidative cyclisation of **77.4** using DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone) gave cyclic PMP acetal **77.5**. The remaining unprotected primary alcohol was then *O*-trityl protected, and the acetal reductively cleaved to give alcohol **77.6**, which was then oxidised using a Swern oxidation reaction to give the desired aldehyde **77.7** (Scheme 77).



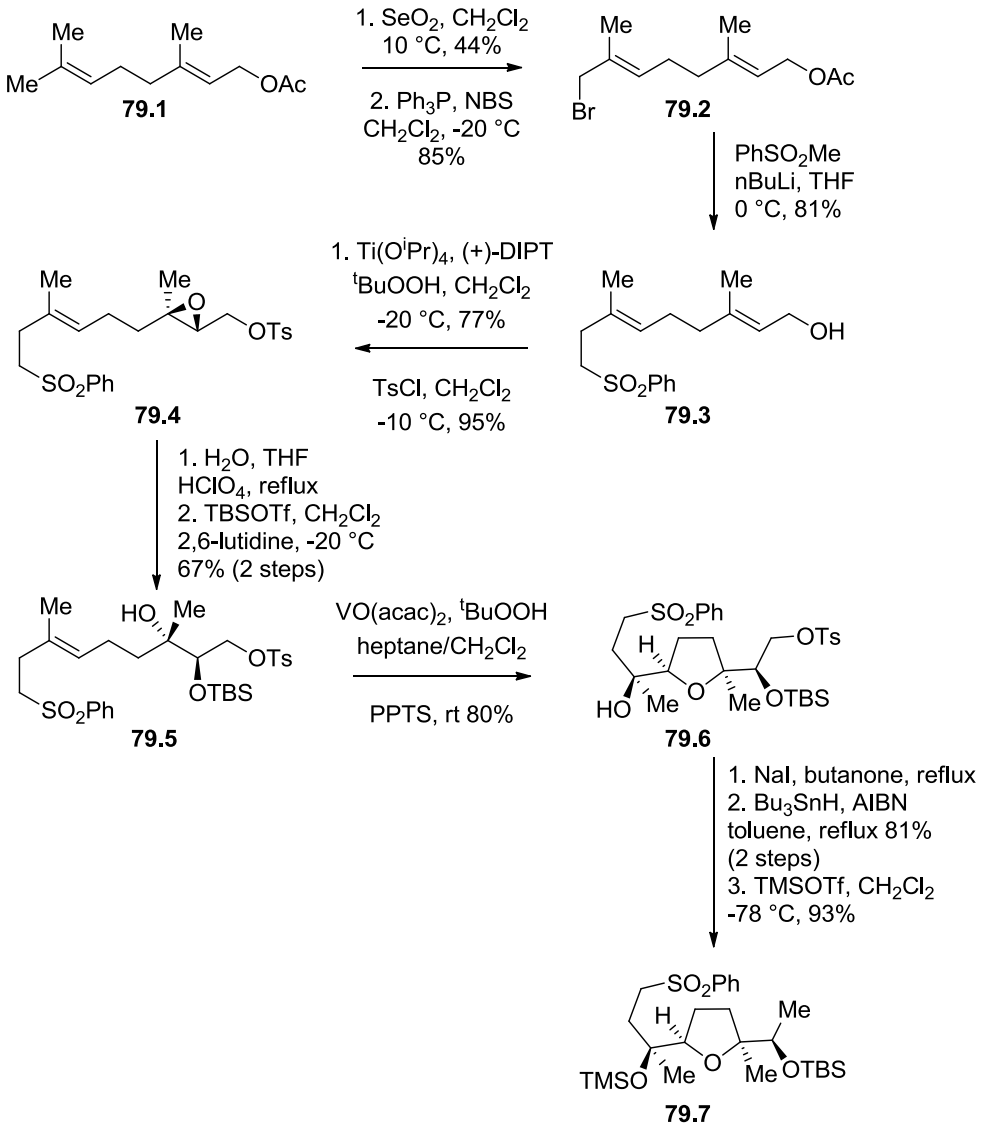
Scheme 77. Synthesis of aldehyde fragment **77.7**[175]

Synthesis of the ketone fragment **78.11** began with the symmetrical unprotected alcohol **78.1** that was also used as a substrate for reductive desymmetrisation. A palladium catalysed asymmetric ring opening reaction afforded diol **78.2** in high yield (80%) and excellent 94% ee. The alcohol groups of diol **78.2** were then selectively protected with silyl and PMB protecting groups to give protected diol **78.3**, with ozonolysis followed by reduction affording acyclic ω-diol **78.4**. Oxidative cyclisation to afford a cyclic PMP acetal, followed by *O*-silyl deprotection gave acetal **78.5**. Treatment of acetal **78.5** with TCDI (thiocarbonyl diimidazole) protected the 1,3-diol fragment to afford cyclic thiocarbonate **78.6**. A radical mediated reduction reaction selectively gave primary alcohol **78.7**; which was then oxidised to its corresponding aldehyde followed by a Wittig reaction to give α,β-unsaturated ester **78.8**. Hydrogenation of **78.8** resulted in both the alkene bond being reduced and cleavage of the PMP acetal to give diol **78.9**. A second thiocarbonate formation and radical catalysed deoxygenation then reaction gave primary alcohol **78.10**. Subsequent oxidation of **78.10**, Grignard addition of MeMgBr and a further oxidation step then gave the desired ketone fragment **78.11** (Scheme 78).



Scheme 78. Synthesis of the ketone fragment **17.11**[175]

The Lautens synthesis also required synthesis of the key furan fragment **79.7**. Its synthesis began with allylic oxidation of the terminal methyl group of geranyl acetate **79.1** using SeO_2, followed by Appel bromination of the resultant alcohol to give allyl bromide **79.2**. Alkylation of the enolate of a sulfone with allyl bromide **79.2** with concomitant removal of its acetate group, gave alcohol **79.3**.Sharpless asymmetric epoxidation reaction and tosyl protection of the primary alcohol afforded tosylate **79.4**. Acid catalysed epoxide ring opening and secondary alcohol *O*-silyl protection then afforded the protected triol **79.5**. A vanadium catalysed oxidative furan ring forming reaction was then carried out to afford tetrahydrofuran **79.6**. Iodination and subsequent radical catalysed dehalogenation was then followed by alcohol silyl protection to give the key sulfone fragment **79.7** (Scheme 79).

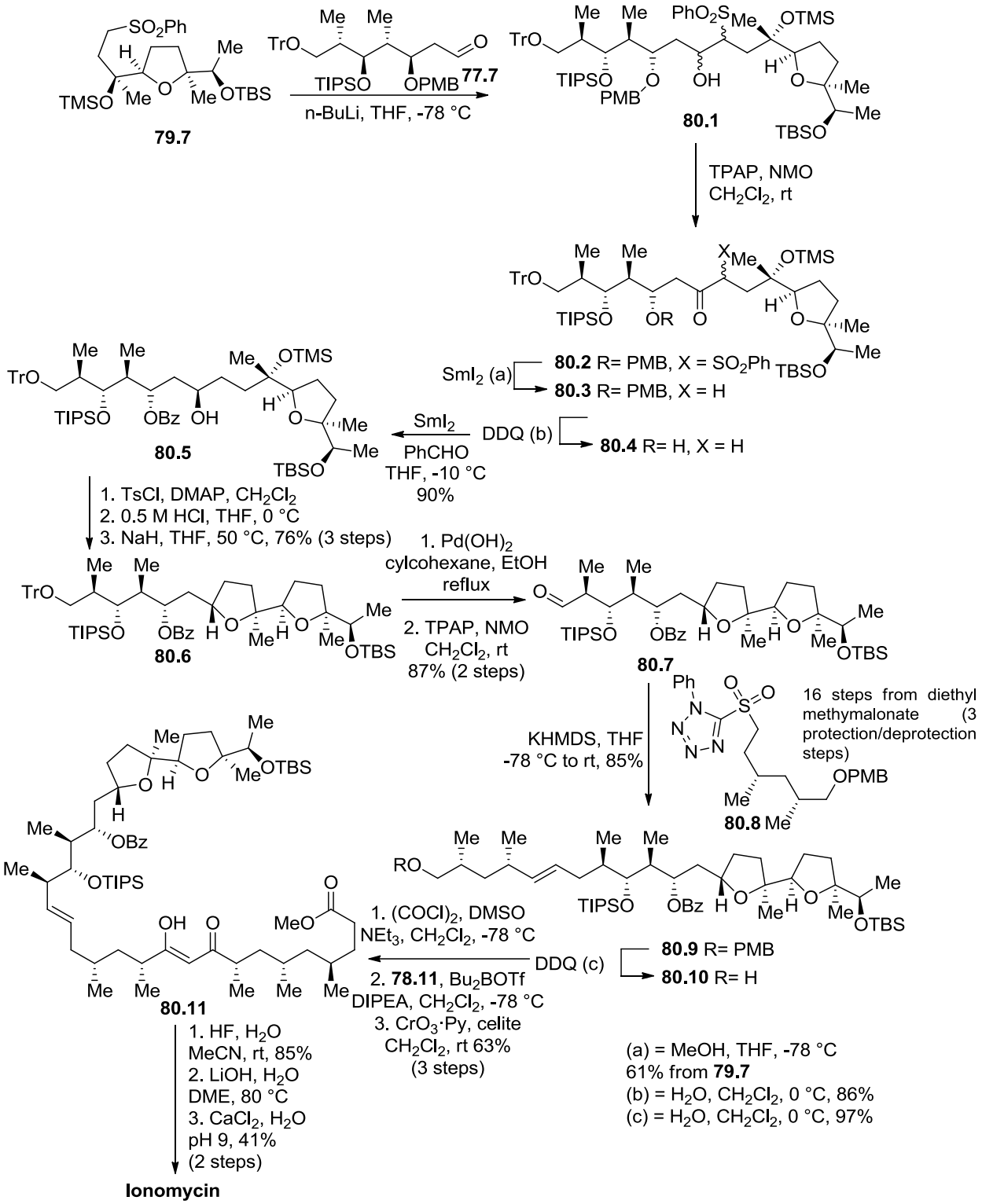


Scheme 79. Synthesis of tetrahydrofuran **18.7**

Once these fragments had been prepared, then they were combined to give ionomycin. The enolate of sulfone **79.7** underwent coupling with aldehyde **77.7** to give the alcohol **80.1** which was then oxidised to afford ketone **80.2**. The sulfone moiety of **80.2** was then reductively cleaved using samarium iodide, followed by DDQ mediated PMB deprotection to obtain alcohol **80.4**. Treatment with samarium iodide and benzaldehyde gave β-hydroxy benzoate **80.5**, with no other regioisomer being formed. The alcohol group of **80.5** was then activated for cyclisation by tosylation, followed by *O*-TMS deprotection, to afford a crude hydroxy tosylate that was treated with sodium hydride to construct the second ring of bis-tetrahydrofuran compound **80.6**. Trityl deprotection, followed by oxidation then afforded aldehyde **80.7**, which underwent a modified Julia coupling with sulfonamide **80.8** to give alkene **80.9**. PMB deprotection of **80.9**

gave alcohol **80.10**, followed by Swern oxidation to a ketone, and aldol coupling with the boron enolate of ketone **78.11,** with a further alcohol oxidation step then affording hydroxy alkene **80.11**. Subsequent removal of the remaining three protecting groups, followed by ester hydrolysis afforded ionomycin (Scheme 80) in a 5.6% overall yield.

While the Lauten synthesis of the complex natural product ionomycin is highly impressive, utilising a wide range of elegant chemistry, the synthetic route is clearly not perfect. It has a heavy reliance on protecting group chemistry, with the use of 25 protection/deprotection steps dramatically increasing the number of synthetic steps and amount of waste and by-products produced. It is also a very redox reliant synthesis, with a large number of oxidation and reduction steps being employed, with a number of redox processes occurring at the same carbon position! During the synthesis of ketone fragment **78.11** there are also two deoxygenation steps to give alcohols **78.7** and **78.10** respectively, with this process involving removal of previously installed stereocentres.



Scheme 80. Synthesis of ionomycin[175]

The recent ionomycin synthesis by the Kocienski group in 2009[176] is similar to the Lautens synthesis with respect to the strategy of assembling ionomycin from four very similar fragments, however, these fragments were obtained in a much more efficient manner (Figure 17).

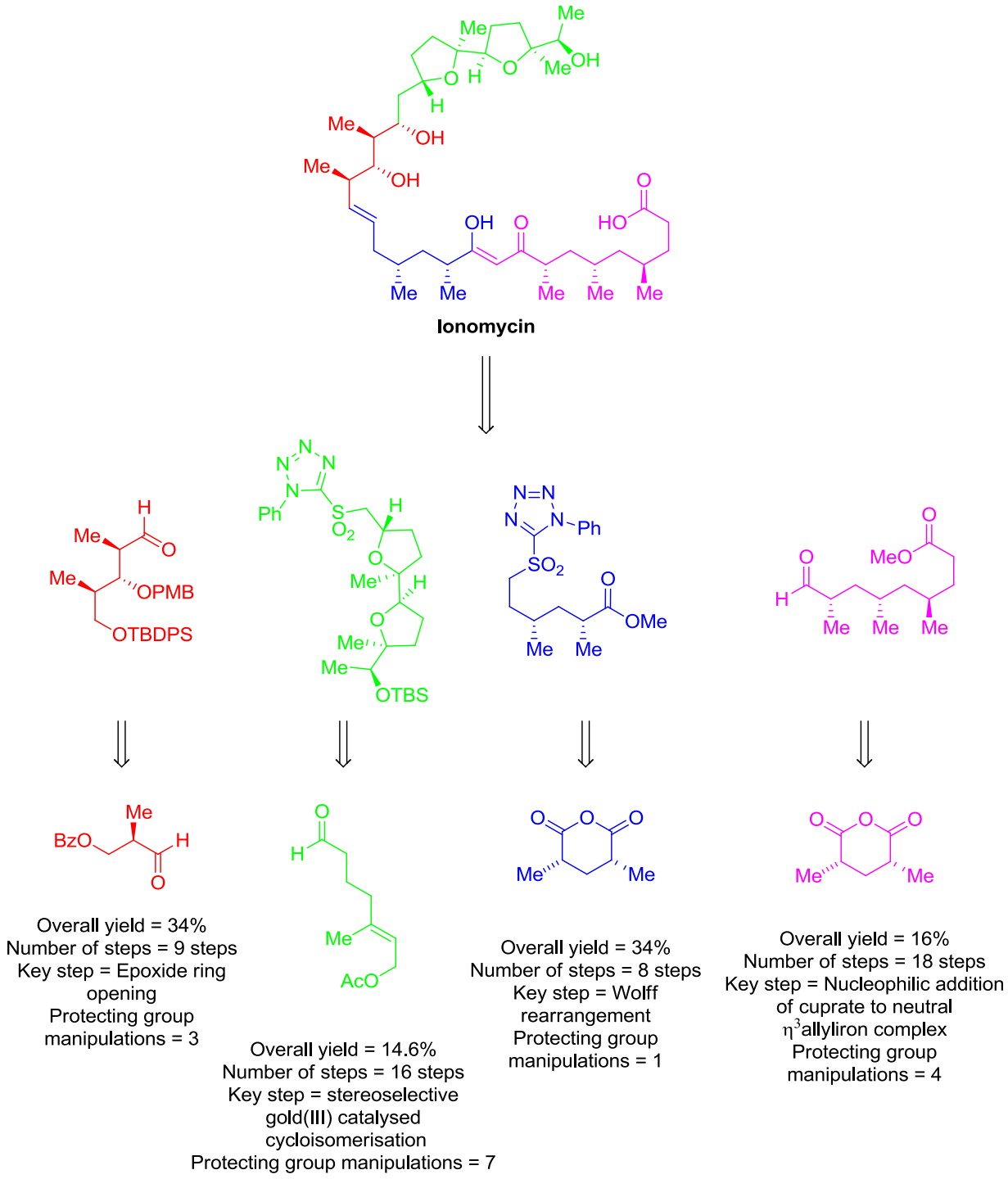
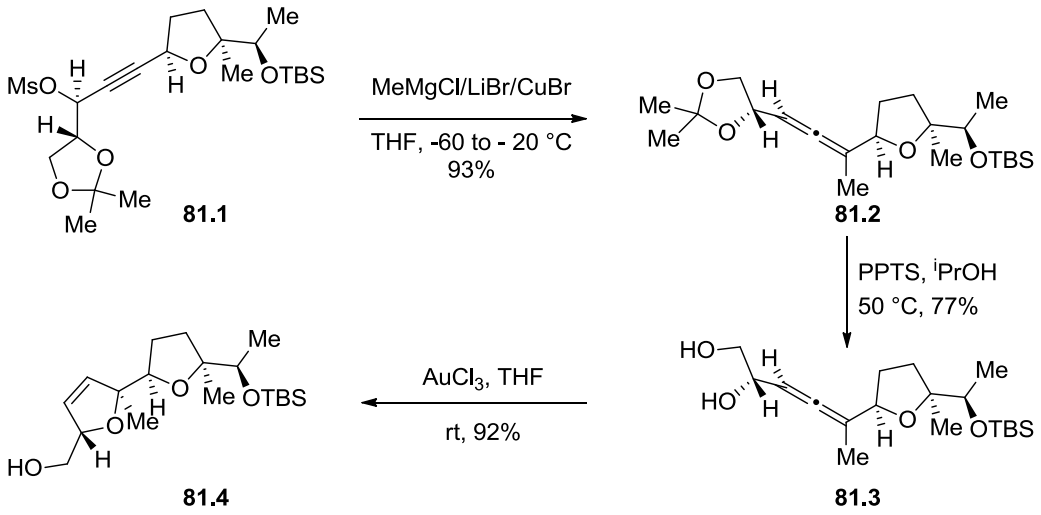


Figure 17. Kocienski retrosynthetic fragmentation of ionomycin[176]

The most impressive fragment synthesis was that employed for the preparation of bis-hydrofuran **81.4**, which was constructed in the following manner. Allene **81.2** was obtained from alkyne **81.1** *via* a stereoselective copper(I)-mediated *anti*-selective S_N2' reaction, which after deprotection of the tetrahydropyranyl group using PPTS (pyridinium *p*-toluenesulfonate) gave diol **81.3**. Diol **81.3** then underwent highly stereoselective gold(III) catalysed cycloisomerisation of its α-hydroxyallene fragment to afford 2,5-dihydrofuran **81.4** (Scheme 81). This catalytic construction of the second hydrofuran ring was far more efficient than approaches employed in previous syntheses (Scheme 79).



Scheme 81. Construction of the bis-hydrofuran moiety by Kocienski[176]

While this synthesis clearly is an improvement upon previous attempts, it still cannot be considered to really provide a viable route for the large scale production of ionomycin, with an overall yield of only 0.68% being achieved over the 33 step synthesis.

5.3 Synthesis of Pironetin

Pironetin (Figure 18) was first isolated independently, by two Japanese groups in 1993 from the fermentation broths of both *Streptomyces sp.* NK10958 and *Streptomyces prunicolor* PA-48153.[178-180] Pironetin is an unsaturated δ-lactone attached to a *syn, anti, syn.* stereotetrad. It was originally of interest due to its plant growth regulatory and immunosuppressive activities, however, more recently it has also been identified as a strong antitumor agent.[181] It has been

synthesised a number of times, the first of which was by Yasui *et al.*[178] in 1995 (shown in red). This first synthesis was then quickly followed by those of Gurjar *et al.* (shown in green)[182] and Chida *et al.* (shown in blue)[183]

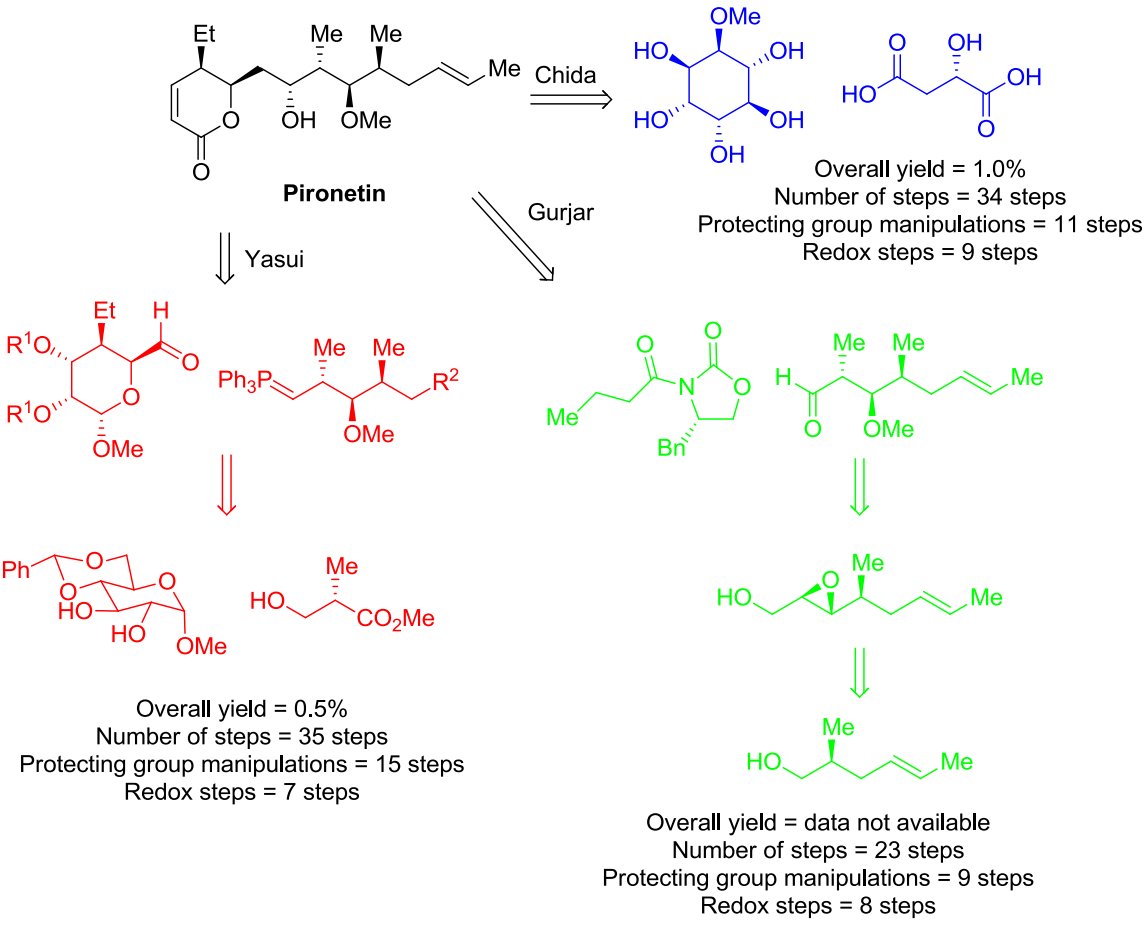
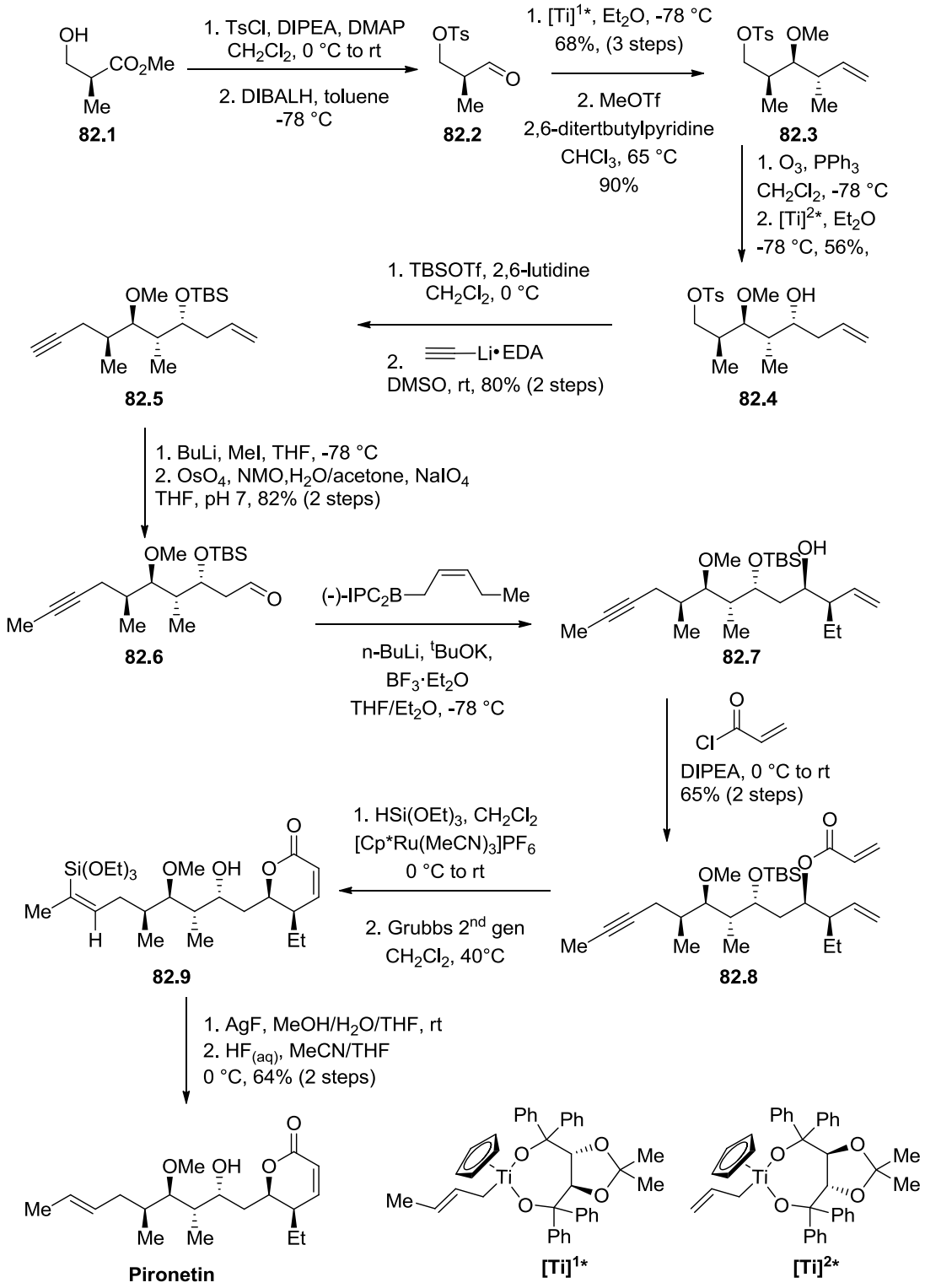


Figure 18. Selected syntheses of Pironetin

A more recent impressive synthesis of pironetin is that by the Cossy group.[181] Compared to previous syntheses it is much more concise, achieving the final product in only 14 steps from the commercially available starting material *(S)*-Roche ester **82.1** (Scheme 82).

(*S*)-Roche ester **82.1** was tosyl protected followed by reduction of its ester functionality with DIBALH which afforded aldehyde **82.2**. This aldehyde was then subjected to a diastereo- and enantioselective crotonylation reaction using chiral titanium complex **[Ti]1*** to generate the homoallylic alcohol, which was subsequently *O*-methylated to give alkene **82.3**. Ozonolysis of

the alkene bond of **82.5** followed by a further diastereoselective allylation reaction using chiral titanium complex **[Ti]^{2*}** gave alcohol **82.4**. *O*-Silyl alcohol protection was followed by treatment with a lithium acetylide ethylenediamine complex to introduce the terminal alkyne functionality of alkyne **82.5**. Once the terminal lithium anion of alkyne **82.5** was methylated, its alkene functionality was dihydroxylated with osmium tetroxide to afford a diol which was then oxidatively cleaved with sodium periodate to give aldehyde **82.6**. A stereoselective boron-mediated pentenylation reaction using cis-2-pentene was then carried out to afford alkene **82.7**, acylation of its alcohol gave bis-alkene **82.8**. The diene functionality of **82.8** then underwent a ruthenium catalysed hydrosilylation reaction, followed by a RCM (ring closing metathesis) reaction and acid mediated protodesilylation to give pironetin in an impressive overall yield of 8.2%



Scheme 82. Cossy synthesis of pironetin[181]

While this is clearly an impressive synthesis there are still a number of steps that are still less than ideal. For example, the two diastereo- and enantioselective crotonylation steps to

obtain **82.3** and **82.4** proceed through the use of a stoichiometric amounts of chiral titanium and boron reagents, which considering their level of complexity and cost would prevent this synthesis from being conducted on a large scale. Furthermore, allylation of **82.2** is immediately followed by ozonolysis, resulting in the cleavage of a C1 carbon fragment, which had previously been installed as part of a C_3-allyl unit. There is also a loss of ethylene associated with the RCM reaction, which also affects the overall atom economy of the synthesis. The synthesis also contains an alkyne hydrosilylation reaction and subsequent protodesilylation step for this RCM strategy to be effective. All of these requirements have a considerable impact on the efficiency and cost of this synthesis, resulting is an overall atom economy for this synthesis of only 6.6%.

5.4 Synthesis of Spirodienal A

Spriodienal A (Figure 19) is a spiroketal that was isolated from fermentation broths of the myxobacteria *Sorangium cellulosum* in 2009,[184] which was shown to exhibit potent antibiotic and cytotoxic activity.[184]

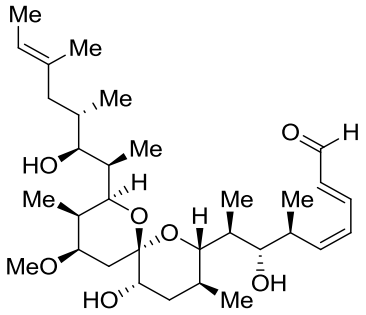
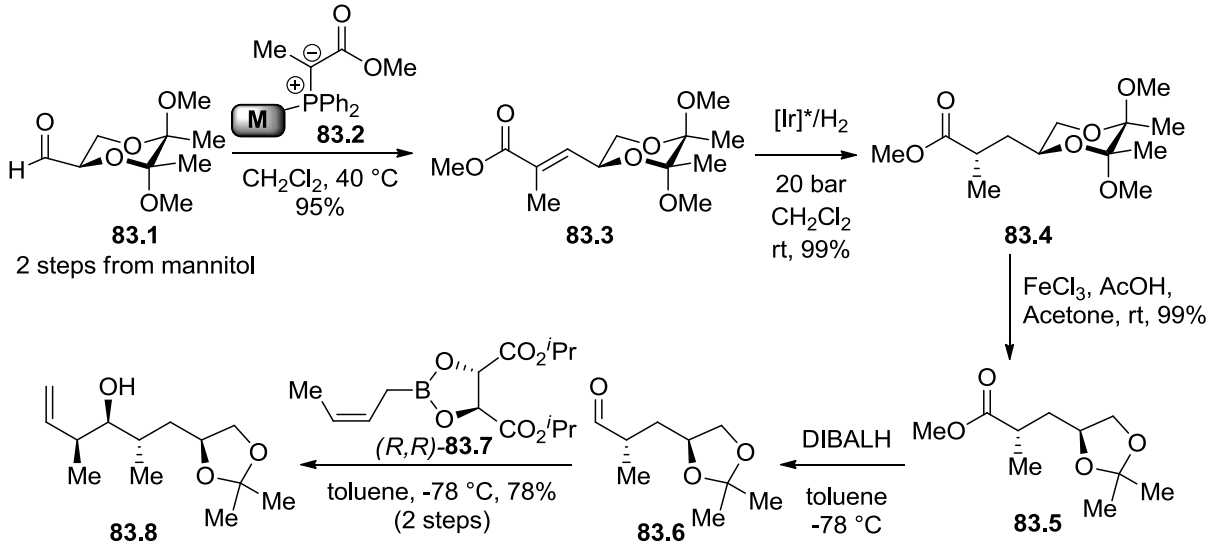


Figure 19. Spirodienal A

The first total synthesis of spirodienal A was completed by the Ley group in 2014.[185] Synthesis was conducted predominantly in flow systems which were proposed to allow for high levels of control and the use of otherwise 'challenging' conditions; including high pressure; the use of gaseous reagents; and the use of highly toxic reagents – all of which led to a highly convergent and efficient approach.[185]

Synthesis began with 2,3-butane diacetal protected aldehyde **83.1** which underwent a solid supported Wittig reaction, where the ylid reagent **82.2** was supported on a monolith. This

approach meant that upon reaction completion, the triphenylphosphine oxide by-product was left attached to the monolith and could be simply filtered off, vastly improving the ease of purification. The resultant α,β-unsaturated ester **83.3**, was then hydrogenated at 20 bar utilising Pfaltz's iridium catalyst to afford methyl ester **83.4**. A protecting group switch led to the formation of acetal **83.5**. The methyl ester of **83.5** was then reduced to aldehyde **83.6** using DIBALH which was immediately reacted with the stoichiometric amounts of chiral tartrate derived crotylation reagent *(R, R)*-**83.7**, to give the key homoallylic alcohol intermediate **83.8**. All of the reactions from aldehyde **83.1** to alkene **83.8** were conducted entirely in flow in an overall 73% yield (Scheme 83).

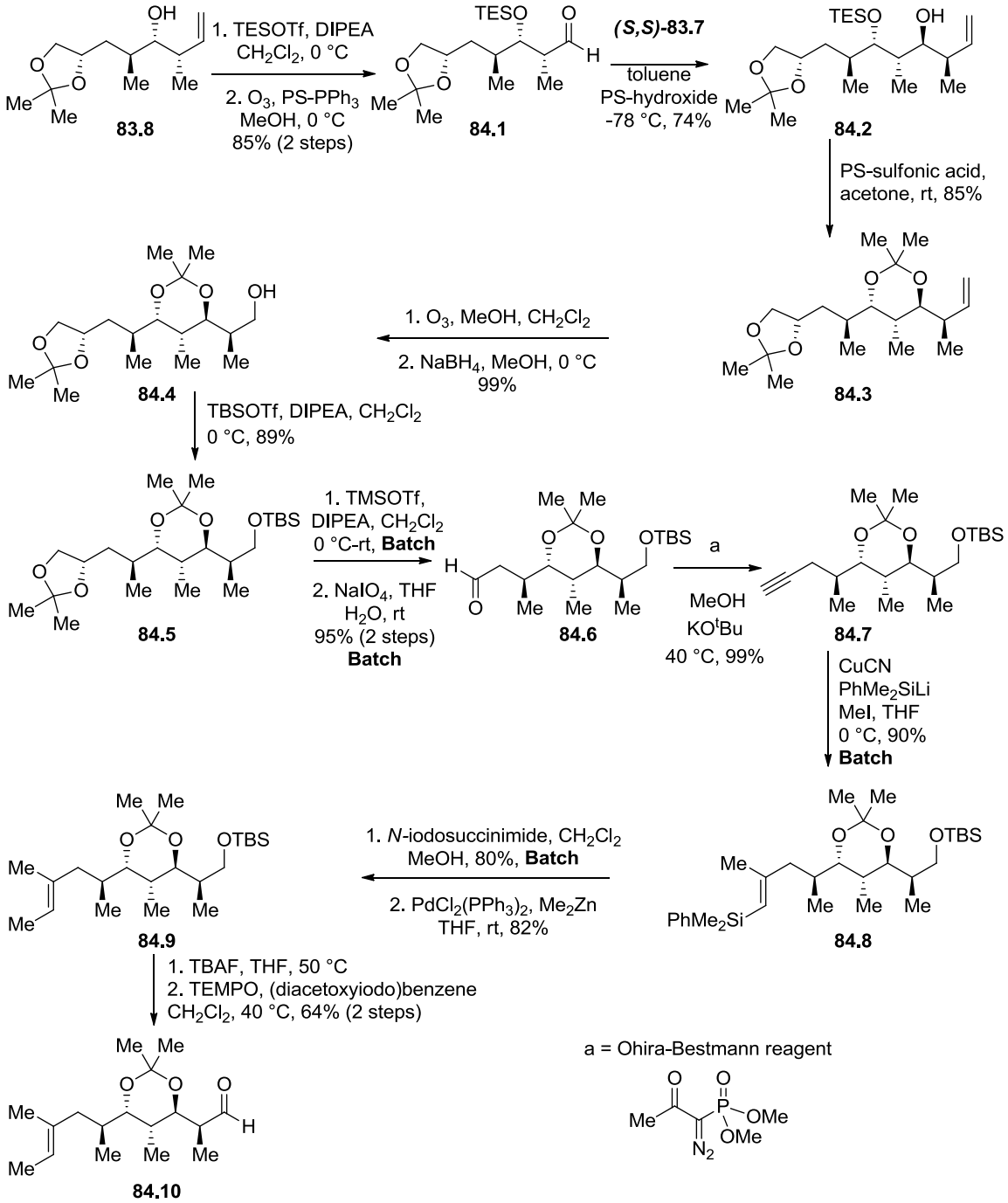


Scheme 83. Flow synthesis of key intermediate **83.8**[185]

With homoallylic alcohol **83.8** in hand, the synthesis then diverged into a parallel synthesis, to form the two coupling partners aldehyde **84.10** and dialkyne **85.8** (Scheme 84 and Scheme 85).

To acquire aldehyde **84.10**, the homoallylic alcohol **83.8** was *O*-silyl protected and then subjected to ozonolysis to give aldehyde **84.1**. This was then reacted with the crotylation reagent *(S, S)*-**83.7** to give the homoallylic alcohol **84.2**. Silyl deprotection and acetal protection of the resultant diol fragment were performed simultaneously through the use of polymer supported sulfonic acid to give the diacetal **84.3**. Ozonolysis, followed by borohydride reduction afforded alcohol **84.4**, which was then *O*-silyl protected to give the fully protected polyol **84.5**. A two-step batch sequence was then required to achieve aldehyde **84.6** involving selective hydrolysis of the

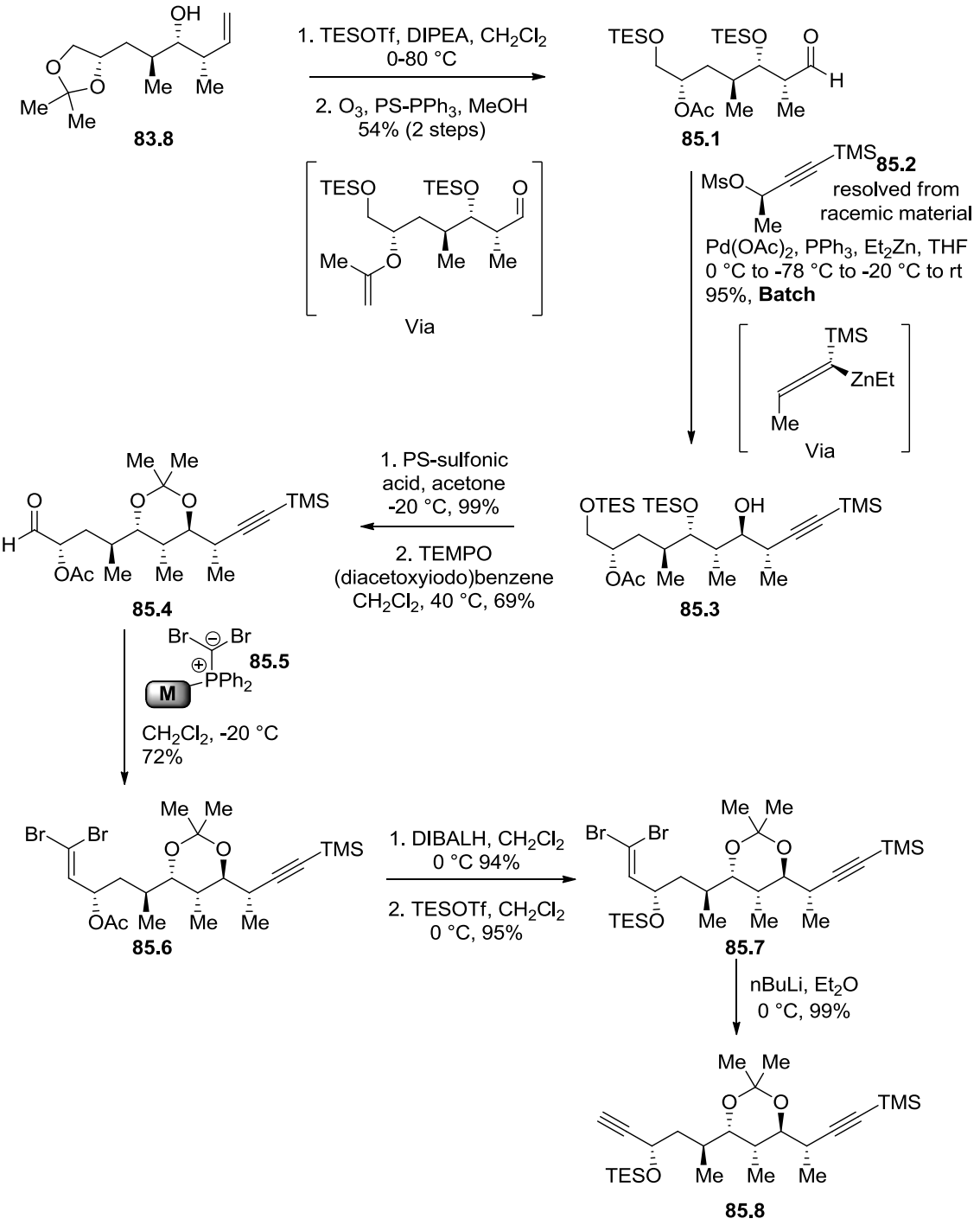
external acetal to afford the corresponding vicinal diol, which then underwent periodate oxidative cleavage to afford aldehyde **84.6**. This aldehyde **84.6** was then subjected to a Seyferth-Gilbert homologation reaction through use of the Bestmann-Ohira reagent (dimethyl (diazomethyl)phosphonate) to afford alkyne **84.7**. A copper catalysed hydrosilylation reaction on **84.7** gave the corresponding alkene **84.8**, which underwent silyl-iodide exchange to give the corresponding allyl iodide, that was then subjected to a Pd(0) mediated Negishi cross-coupling with Me_2Zn to give alkene **84.9**. Silyl deprotection of **84.9** was followed by TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl) catalysed oxidation to afford the desired aldehyde **84.10** (Scheme 84).



Scheme 84. Flow synthesis of coupling partner **84.10**[185]

O-Silyl protection of intermediate homoallylic alcohol **83.8** with TESOTf/DIPEA resulted in cleavage of the acetonide ring to afford a primary silyl protected alcohol and secondary enol ether *in situ* (of the acetonide). The resulting alkene was then subjected to ozonolysis to oxidatively cleave the enol ether and terminal alkene to afford aldehyde **85.1**. Propargylic

mesylate **85.2** was then used as a substrate to generate a chiral allenylzinc reagent *in situ* which was reacted with aldehyde **85.1** through an SE2' mechanism to afford alkyne **85.3**. Silyl deprotection using polymer supported sulfonic acid and selective protection of the two secondary alcohols *via* acetal formation, was followed by a TEMPO oxidation of the terminal alcohol to afford aldehyde **85.4**. A monolith supported Wittig olefination was then carried out to afford dibromo alkene **85.6**. Reductive acetate cleavage followed by further silyl deprotection afforded acetal **85.7**, which upon treatment with n-BuLi gave the desired bis-alkyne functionality of **85.8** *via* a Corey-Fuchs reaction (Scheme 85).

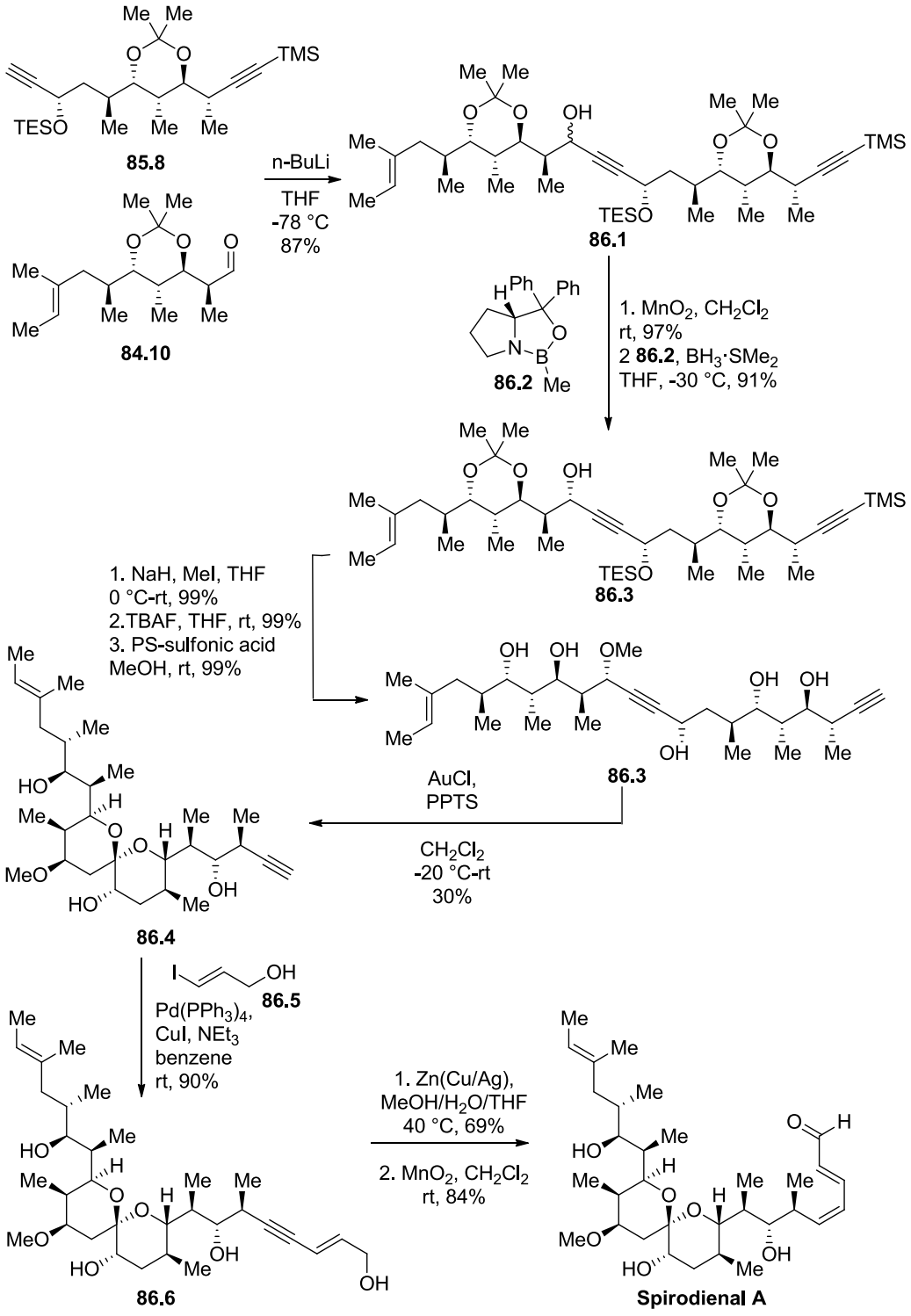


Scheme 85. Synthesis of coupling partner **24.8**[185]

Of all the previous steps used to the coupling intermediates, all except 5 tranformations were conducted in flow (marked in schemes), however, some synthetic steps were unable to be conducted in flow and were instead completed using traditional “batch” conditions. However, it can also be argued that this synthesis represents one of the worst cases of the ‘abuse’ of protecting group usage, with 14 of the 26 synthetic steps used to generate coupling

intermediates **84.10** and **85.8** involving either formation or removal of a protecting group! There are also 10 oxidation/reduction reactions, and this along with the high use of protecting groups, obviously has a huge detrimental effect on the efficiency and sustainability of the synthesis.

The synthesis of spirodienal A was completed through the use of the following batch techniques. Treatment of the bis-alkyne **85.8** with n-BuLi followed by addition of aldehyde **23.10** gave alcohol **86.1**, which was subsequently oxidised to the ynone and stereoselectively reduced using the chiral Corey-Bakshi-Shibata reagent **86.2**. The chiral ynol was then methylated followed by global deprotection *via* sequential treatment with TBAF and a polymer supported acid to afford pentol **86.3**. Spiroketalization was then induced using gold catalysis to give spiroketal **86.4** in only moderate yield (30%). This kind of low yield towards the end of a natrual product synthesis can be disastrous, as it results in the loss of 70% of painstakinly made material. Spiroketal **86.4** then underwent a Sonogashira reaction with vinyl iodide **86.5** to give alcohol **86.6**. Which was subjected to a mixed metal (Zn/Cu) catalysed *cis*-selective alkyne reduction reaction to afford a diene fragment, followed by alcohol oxidation to afford the aldehyde functionality of spirodienal A (Scheme 86).



Scheme 86. Spirodienal A synthesis[185]

This synthesis of spirodienal A was conducted in a divergent manner to try and maximise efficiency by which analogues of the parent natural product could be synthesised. This synthesis by the Ley group is an exciting example of modern natural product synthesis that illustrates the

potential of using flow synthesis for the preparation of complex molecules. However, the use of these expensive flow-systems is currently limited to academia and research labs. With few syntheses having been reported 'on-scale'. Furthermore, their use can be restrictively expensive, with liquid-liquid extraction equipment being expensive and having a high running cost, whilst optimisation of flow transformations can be lengthy and consume a lot of substrate. A necessity of flow chemistry is the use of scavenger or polymer supported reagents to ensure that material of sufficient purity is available to be taken on to the next step. This potentially creates a stoichiometric amount of waste, and whilst these scavenger and polymer supported reagents can be regenerated, these processes often comes with a large energy and commercial cost.

6.0 Conclusion

Huge advances have been made since the dawn of natural product synthesis, with organic chemists given enough time, resource and manpower now being able to synthesise even the most complex molecules. However there is still room for improvement, particularly in the efficiency of reactions, and design of syntheses to embrace the ethos of sustainable chemistry, with the aim of minimising the number of protection/deprotection steps and maximising the number of catalytic rather than stoichiometric reactions used. There are also a number of other aspects that should be considered when trying to move towards a "perfect" synthesis. These include minimising the number of redox steps, maximising yield, use of biorenewable substrates, development of convergent synthetic strategies, invention of new reactions, and the target of crystalline intermediates to facilitate purification. A focus should also be placed on performing reactions at room temperature, under atmospheric conditions using "green" solvents.[109]

7.0 A Protecting Group Free Strategy towards the Sustainable Synthesis of Polypropionate Fragments

7.1 Results and Discussion

Organic synthesis has evolved immensely over the last 100 years to afford an impressive arsenal of reactions and techniques for the synthesis of a wide range of complex molecules. As described in the preceding chapter, this has led to many 'state-of-the-art' syntheses of important medicinally active compounds that can be considered to be at the forefront of 21st century scientific development. However, despite the elegance of many of these synthetic protocols, methods for the synthesis of polyketide derivatives are far from optimal, with multistep synthetic routes often requiring protecting groups, stoichiometric and/or undesirable reagents, and harsh reaction conditions that afford low yields.[98, 109, 172]

This offers the opportunity to develop alternative more efficient 'protecting group free' strategies for the synthesis of chiral building blocks for polyketide natural products. As mentioned earlier a key structural feature of polyketides are the presence of polypropionate (stereotetrad) fragments, with these structural motifs having been the target of a number of synthetic methodologies (Figure 20). One of the most important of these is the aldol reaction, with extensive work by Evans[186-190] and Paterson[191-194] allowing for regio-, stereo-, and enantioselective carbon-carbon bond forming reactions to be performed under either chiral auxiliary or substrate control (e.g. through the use of boron enolates for Evans aldol reactions and for Paterson *anti*-aldol reactions). A further use of the aldol reaction is the Mukaiyama aldol addition,[195] utilising silyl enolates of ketones that add to aldehydes with excellent levels of stereocontrol.

As well as the aldol reaction there are a number of other well established methodologies for the construction of polypropionate fragments, including, the reductive aldol reaction,[196-200] crotylation,[201-208] allenylation,[209-212] epoxide ring opening,[213-216] thiopyran chemistry,[217, 218] [2+2] cycloaddition reactions,[219-223] and sequential substitution reactions (Figure 20).[224-227]

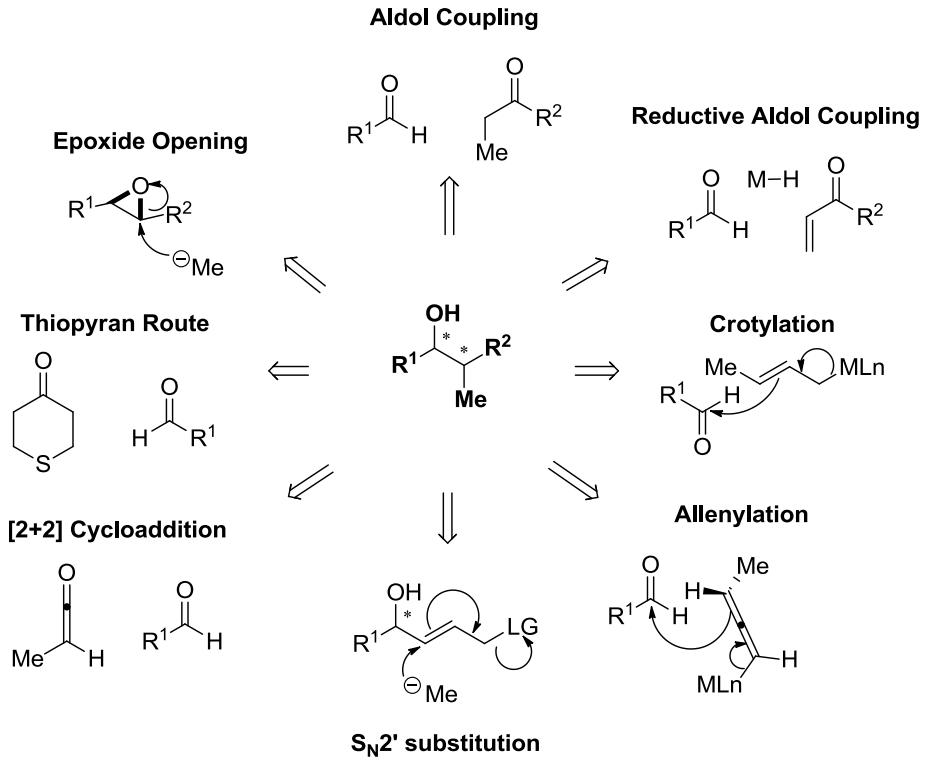
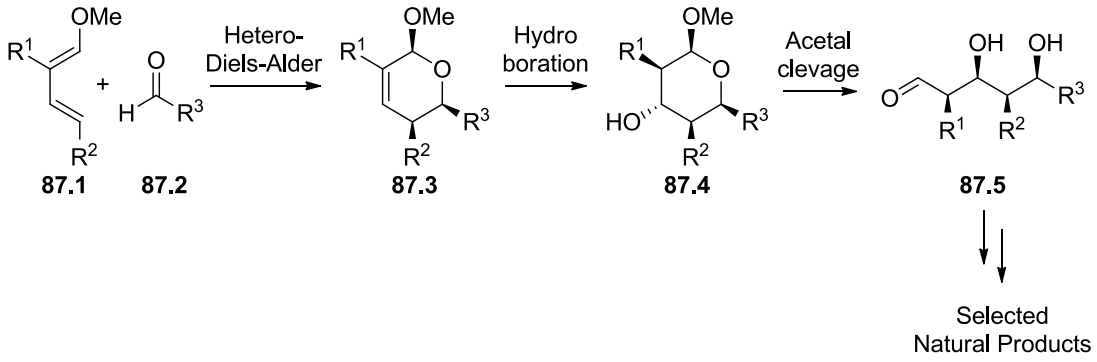


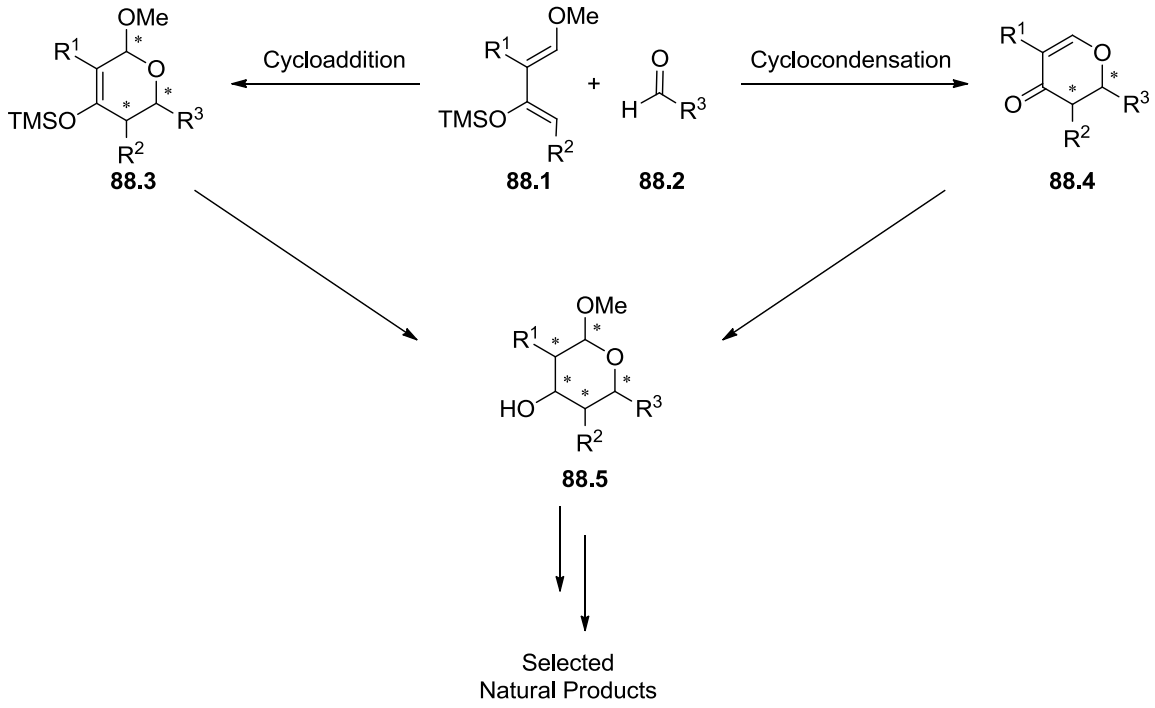
Figure 20. Established methodology for the synthesis of polypropionate fragments[228]

The aim of this project was to develop a sustainable synthetic route to polyketide natural product fragments using a protecting group free strategy. Based on the use of a Lewis acid (LA) catalysed enantioselective hetero-Diels-Alder (HDA) reaction to construct a six-membered dihydropyran ring. This ring could then be derivatized in a number of ways, one of which would be hydroboration to afford a chiral pyran as a masked stereotetrad containing four contiguous stereocentres that was ideally suited for natural product synthesis (Scheme 87). It was envisaged that derivatisation of dihydropyran **87.3** using a range of different chemistries would result in a range of useful chiral building blocks. These could then be used for the synthesis of a range of polyketide natural products (and their analogues), in a “plug and play” manner.



Scheme 87. Proposed hetero-Diels-Alder strategy for the synthesis of polyketide fragments

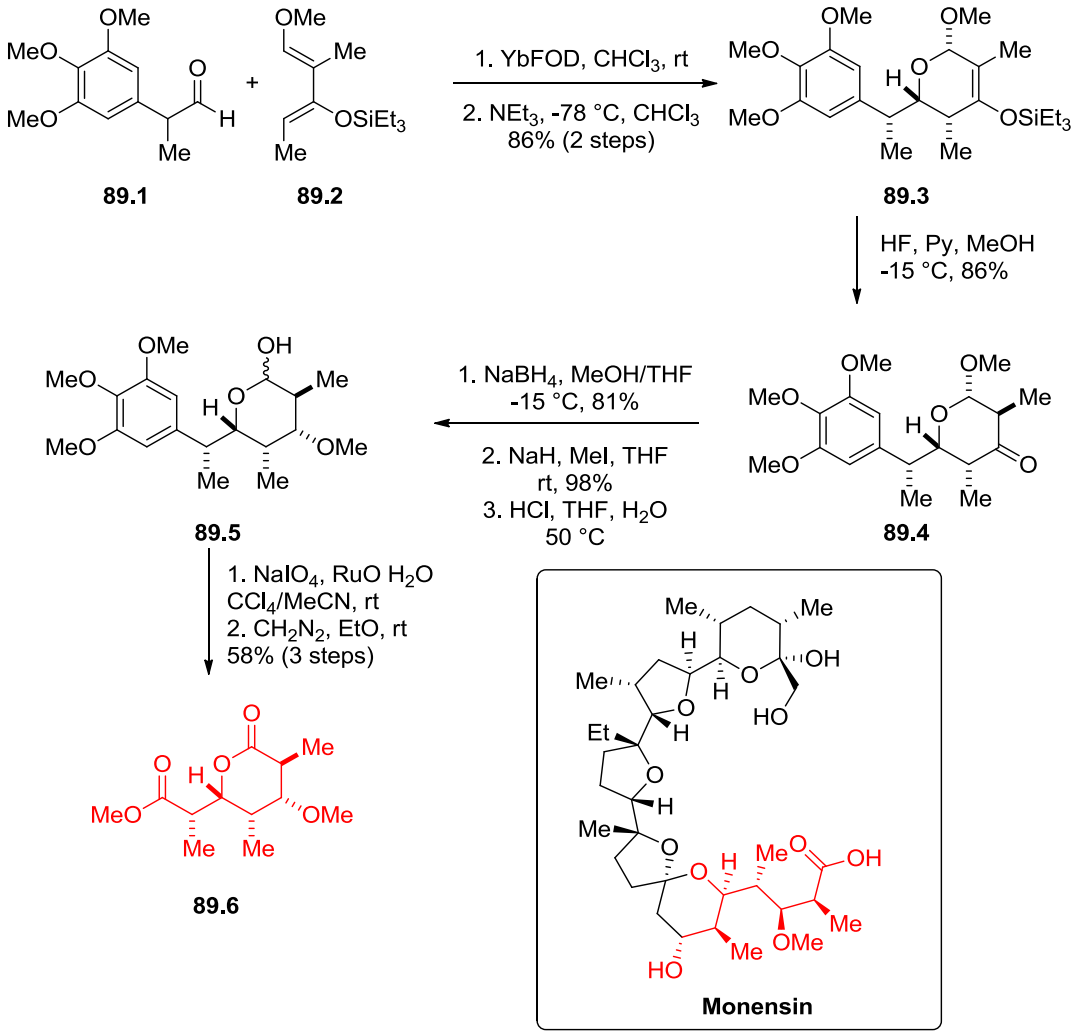
This strategy was inspired by some of the ground breaking work carried out by the Danishefsky group. Their work also focused on development of new synthetic methodology for the synthesis of polyproionates, based on cyclo-addition reactions of Danishefsky type dienes **88.1** with an appropriate aldehyde, which gave rise to silyl enol ether **88.3**, or α,β-unsaturated ketone **88.4**. They showed that application of a series of selective derivatisation reactions to **88.3** and **88.4**, enabled a series of highly functional pyran rings **88.5**, containing four chiral centres to be prepared (Scheme 88).



Scheme 88. Danishefsky's strategy for the synthesis of polypropionates[229, 230]

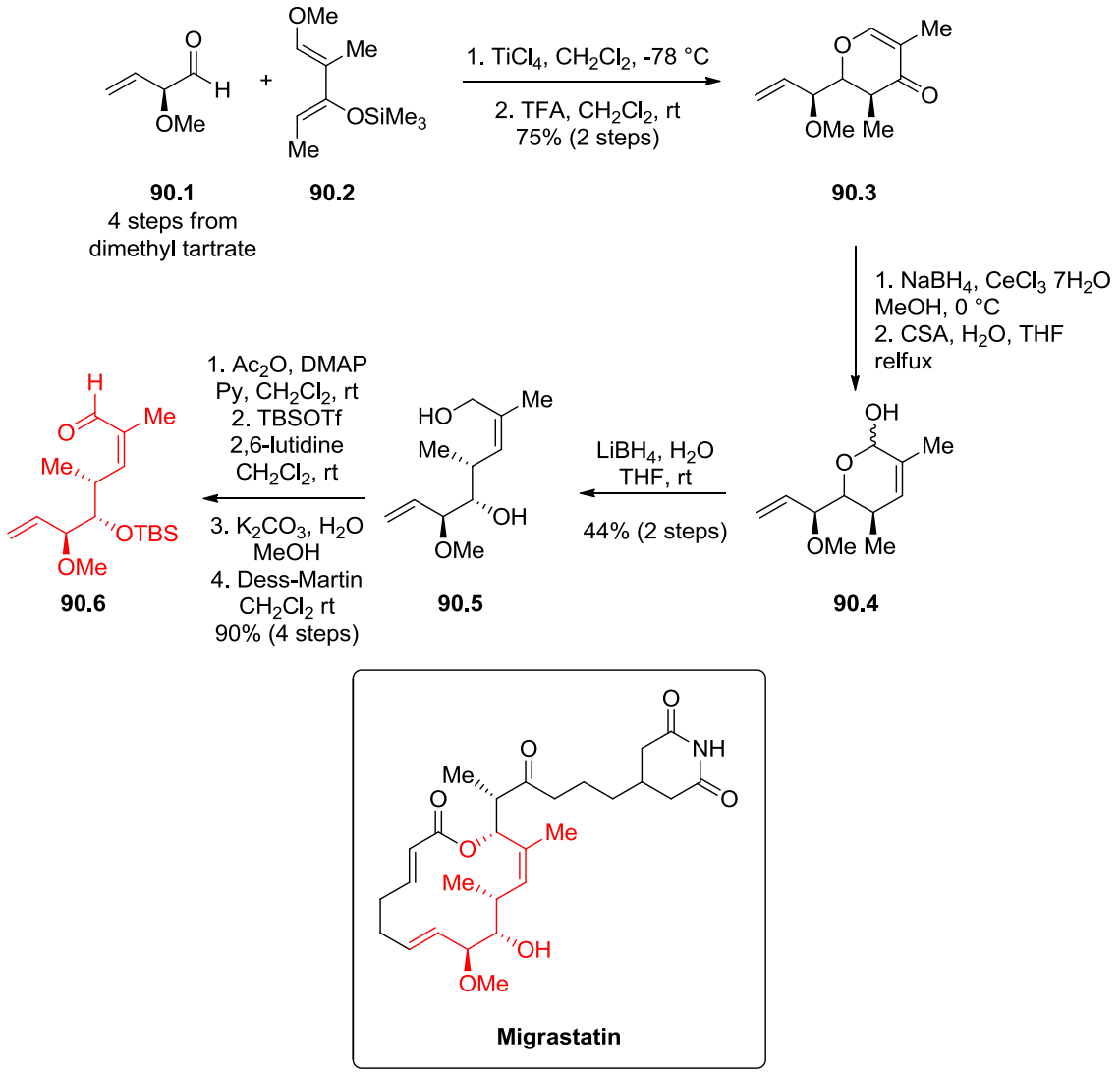
This elegant methodology has since been applied to a range of syntheses, including complex polyketide natural products and saccharides, where stereochemical control is achieved through derivatisation of cyclic structures using simple reagents, which would not be possible using an acyclic substrate.[229-241] Once the derivatized pyran has been constructed cleavage of the ring can be easily achieved by exploiting the masked aldehyde character of the hemi-acetal linkage. "*Hence both the construction and the disassembly of the cyclic edifice need not add steps to the total program and, therefore, need not be regarded as contrivances*" (S. Danishefski).[229] Two examples of where this methodology has been applied for the synthesis of polypropionate fragments towards natural product synthesis are shown below.

The first example is the synthesis of lactone **89.6**, which is a subunit of monensin (a polyether antibiotic). A ytterbium catalysed cycloaddition reaction of aldehyde **89.1** and Danishefsky diene **89.2**, affords silyl enol ether **89.3**. Treatment of **89.3** with HF resulted in silyl deprotection to afford ketone **89.4**, which was then reduced to its corresponding alcohol. Methylation of this alcohol followed by acetal cleavage gave lactol **89.5**. Treatment of lactol **89.5** with catalytic ruthenium dioxide in the presence of $NaIO_4$ afforded a crude lactone acid which was then esterified with diazomethane to afford racemic lactone **89.6** (Scheme 89).



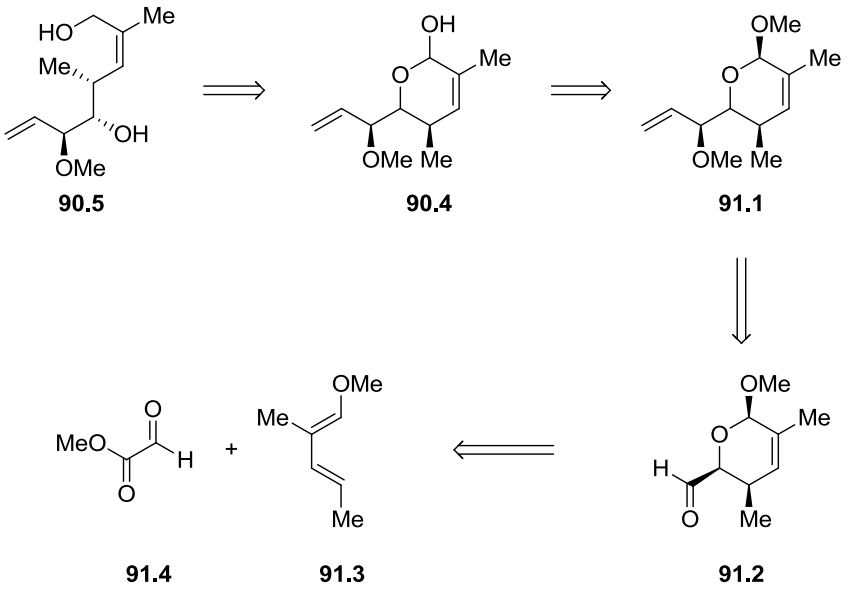
Scheme 89. Synthesis of racemic polypropionate fragment **89.6**[229]

A second selected example is the synthesis of aldehyde **90.6**, as a masked polypropionate fragment present in migrastatin, which is a natural product that has anti-cancer properties. A titanium catalysed diene aldehyde cyclocondensation reaction of aldehyde **90.1** (4 steps from dimethyl tartrate) and Danishefsky diene **90.2** gave α,β-unsaturated ketone **90.3**. Luche reduction of ketone **90.3** afforded an allylic alcohol which underwent an aqueous Ferrier arrangement to give lactol **90.4.** Reduction of lactol **90.4** with $LiBH_4$ afforded the acyclic diol **90.5**, with selective acetate protection of the primary alcohol functionality being followed by *O*-silyl protection of the secondary alcohol. Acetate removal and subsequent alcohol oxidation then afforded the core polypropionate fragment **90.6** (Scheme 90).[239]



Scheme 90. Substrate controlled synthesis of polypropionate fragment **90.6**[239]

It was proposed to modify this powerful methodology for the synthesis of a range of complex enantiomerically enriched pyran based building blocks, that could be accessed in a highly efficient manner, that would be ideally suited for the synthesis of polyketide natural products through a "plug and play" approach. If the structure of the advanced alcohol intermediate **90.5** is considered, then a retrosynthetic analysis can be performed to highlight how our proposed methodology was envisaged to proceed. Lactol **90.4** could potentially be accessed from dihydropyran **91.1**, with the presence of the terminal alkene allowing for late stage derivatisation. This alkene unit could be introduced *via* addition of a vinyl Grignard reagent to the corresponding aldehyde **91.2**. Aldehyde **91.2** could then be accessible directly from an enantioselective HDA reaction of 1-alkoxy diene **91.3** with methyl glyoxalate, the ester group of which would function as a synthetic handle for subsequent derivatization (Scheme 91).



Scheme 91. Retrosynthetic analysis of alcohol **90.5**

7.2 Diene Synthesis

The diene **91.3** shown below (Figure 21) was identified as the target starting material for this methodology, however, a review of the literature revealed that routes for the preparation of 1-alkoxy dienes were somewhat limited. This resulted in the synthesis of this target diene becoming problematic, and significant effort was expended to identify an efficient route for their synthesis.

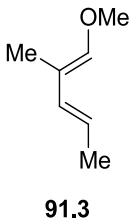
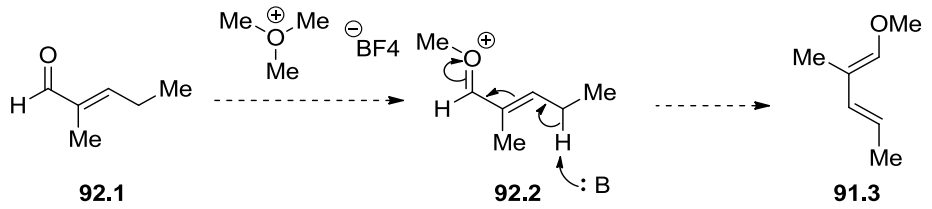


Figure 21. Target diene **91.3**

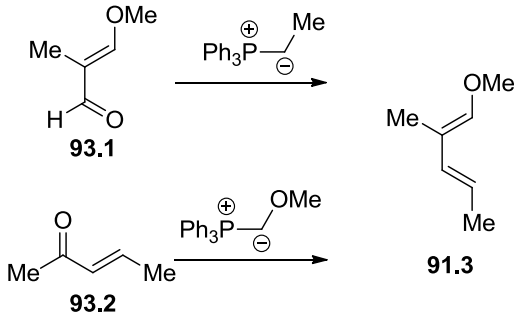
Initial attempts were based on the use of a strong electrophilic methylating agent, such as Meerwein's salt (Me_3OBF_4), which we hoped would react with the α,β-unsaturated aldehyde

in the presence of base, to form the desired enol ether. However, this proved to be unsuccessful with no product formation being observed *via* ^{1}H NMR analysis (Scheme 92).



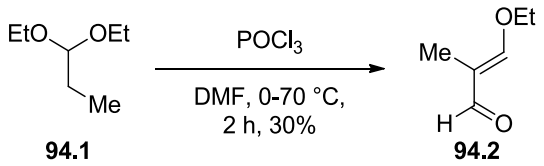
Scheme 92. Unsuccessful synthesis of diene **91.3**

Multiple attempts were made along these lines with no success, with attempts at other elimination strategies also proving fruitless. Examination of the literature revealed that one successful approach for the synthesis of small diene molecules was the use of Wittig olefination.[242] From this precedent, two carbonyl species were identified as potential targets, **93.1** and **93.2**, with the aim of using them as substrates for a Wittig olefination reaction to obtain the desired diene **91.3** (Scheme 93).



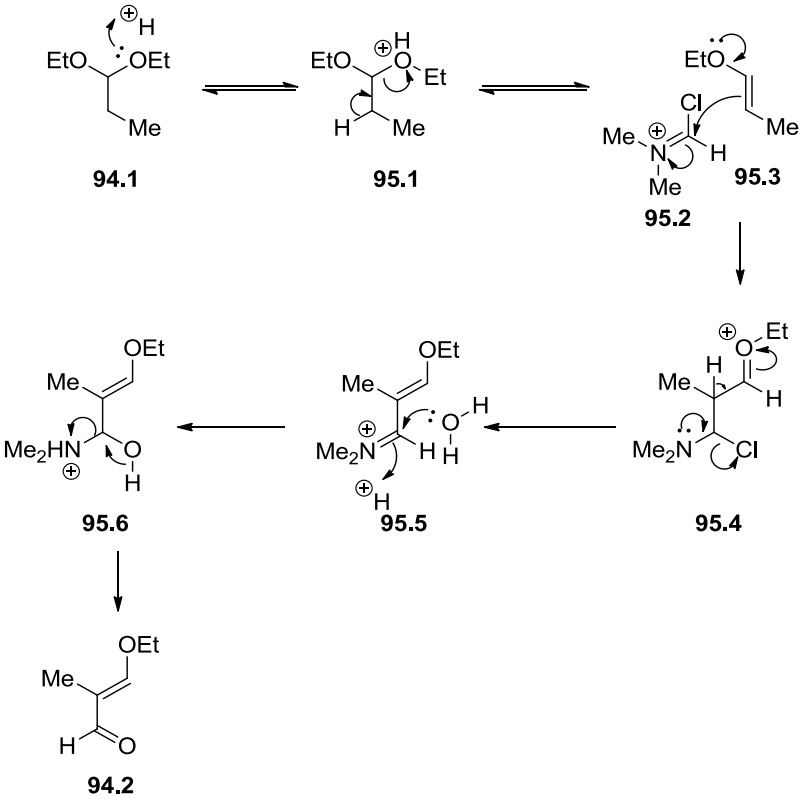
Scheme 93. Proposed Wittig synthesis of diene **91.3**

It was decided proceed with diene synthesis using an anolouge of aldehyde **93.1**, since protocols for the synthesis of 3-ethoxy-2-methyl-2-propenal **94.2** were known in the literature. 3-Ethoxy-2-methyl-2-propenal **94.2** was formed by the reaction of propionaldehyde diethyl acetal **94.1** with $POCl_3$ *via* a Vilsmeier-type reaction (Scheme 94).[243, 244]



Scheme 94. Synthesis of 3-ethoxy-2-methyl-2-propenal

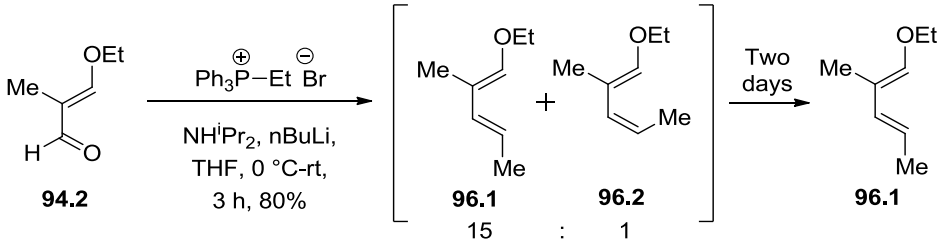
This reaction is proposed to proceed *via* a similar mechanism to the classical Vilsmeier reaction. Protonation of acetal **94.1** is followed by elimination of ethanol to give vinyl ether **95.3**, which then reacts with chloroiminium **95.2**, to afford oxonium **95.4**. This oxonium spicies **95.4** then eliminates chloride to give iminium species **95.5**, which is then hydrolysed to afford aldehyde **94.2** (Scheme 95).



Scheme 95. Mechanism of Vilsmeier reaction

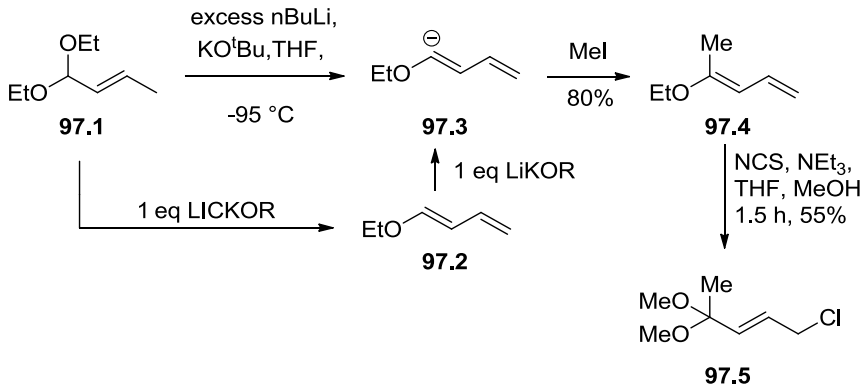
In our hands, formation of aldehyde **94.2** proceeded with 100% *E*-selectivity, with this aldehyde then being carried forward to complete the desired diene synthesis *via* Wittig

olefination with ethyltriphenylphosphonium bromide in the presence of LDA as a strong base. Purification by distillation gave the desired diene **96.1** in good yield and in a ratio of 15:1 (*1E,3E*):(*1E,3Z*), as assigned by ^{1}H NMR spectroscopic analysis (*E, E*)-isomer (δ 5.45 (qd, J = 6.6, 15.1 Hz, 1 H, CH=C*H*CH_3)) (*E, Z*)-isomer (δ 5.31 (qd, *J* = 7.2, 11.7 Hz, 1 H, CH=C*H*CH_3)). However, to our delight, when this mixture of geometric isomers was left at room temperature for two days, it was found to equilibrate in favour of its thermodynamically favourable (*1E,3E*)-isomer in a ratio of 50:1.



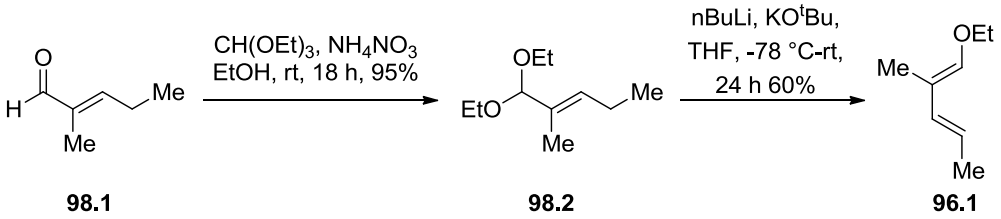
Scheme 96. Synthesis of (*1E,3E*)-1-ethoxy-2-methylpenta-1,3-diene

Concurrent to the syntheses described above, an alternative synthetic strategy to diene **96.1** was investigated. An interesting report from the literature caught our attention involving the synthesis of acetal and carbonyl substituted allyl chlorides from α,β-unsaturated acetals,[245] which was proposed to proceed through alkoxy diene **97.2** (Scheme 97). It was reported that treatment of α,β-unsaturated acetal **97.1** with an excess of n-butyl lithium and potassium *tert*-butoxide (known as LICKOR), afforded diene **97.2**, which in the presence of excess base and methyl iodide gave the substituted diene **97.4**. Addition of *N*-chlorosuccinimide, base and methanol then gave the acetal substituted allyl chloride **97.5**.



Scheme 97. Synthesis of acetal substituted allyl chloride **97.5**[245]

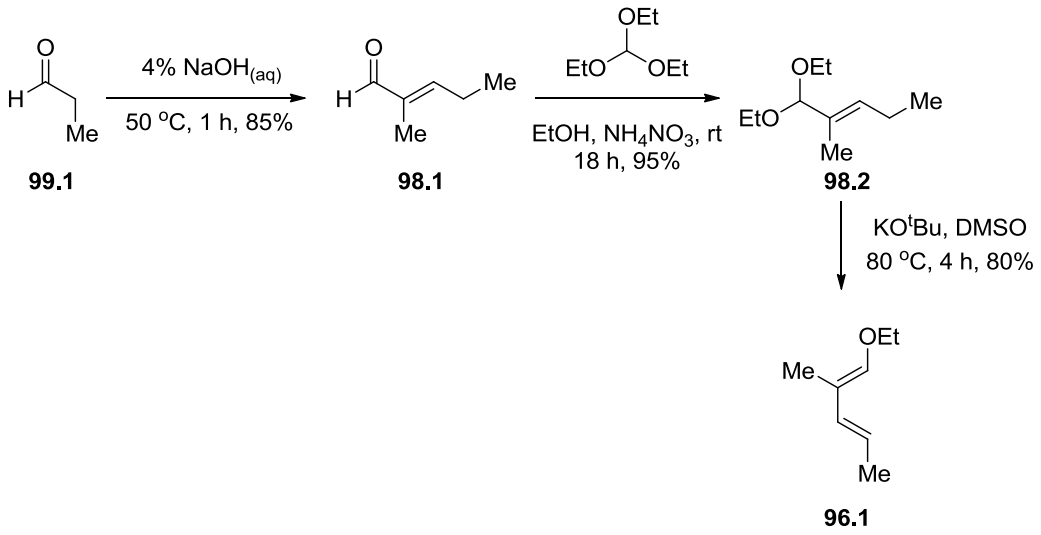
It was hoped that the first step of this methodology (**97.1** to **97.2**) could be applied for the synthesis of our target diene **96.1**. Therefore, synthesis of α,β-unsaturated acetal **98.2** from α,β-unsaturated aldehyde **98.1** was achieved through treatment of α,β-unsaturated ketone **98.1** with triethyl orthoformate and ammonium nitrate, in 95% yield. The conditions of the LICKOR mediated elimination reaction were adjusted for use with α,β-unsaturated acetal **98.2**; with increased amounts of base, extended reaction time and elevated temperatures required, when compared to the literature procedure (Scheme 98). Diene **96.1** was isolated in 60% yield, affording a second viable route to the necessary diene. This route proved to be a significant improvement, with many of the reagents employed for synthesis accessible from biorenewable starting materials.



Scheme 98. Alternative synthesis of (*1E,3E*)-1-ethoxy-2-methylpenta-1,3-diene

For example, propionaldehyde **99.1** is readily obtained from biorenewable propanol. Consequently, an aldol self-condensation reaction was carried out to afford α,β-unsaturated aldehyde **98.1** in 85% yield, with the reaction proceeding as a biphasic mixture, allowing for easy work up and purification. Acetal formation was achieved in the same manner as above, through

the use of ammonium nitrate which is commonly used as a high nitrogen fertiliser, and as such is available at large quantities and in low cost. More benign conditions were then developed to carry out elimination of **98.1** to **96.1**. It has been reported that use of solutions of potassium *tert*-butoxide in dimethyl sulfoxide results in a highly basic system.[246, 247] This is believed to occur due to the solvent strongly complexing with the potassium cations, producing an activated ligand-separated and dissociated *tert*-butoxide anion in a medium of high dielectric constant.[246] This base system is known to be a powerful reagent for carrying out β-elimination reactions,[246, 247] and its application to the elimination of **98.2** proved successful affording diene **96.1** in 80% yield (Scheme 99).

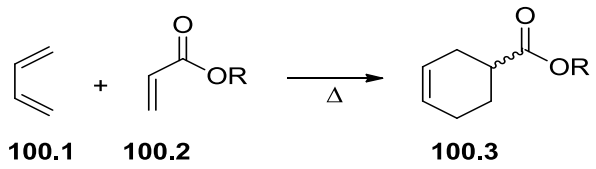


Scheme 99. Synthesis of diene **96.1** from biorenewable sources

With diene **96.1** obtained in synthetically useful quantities, our attention then turned to development of asymmetric hetero-Diels-Alder methodology to synthesise dihydropyran **87.3**.

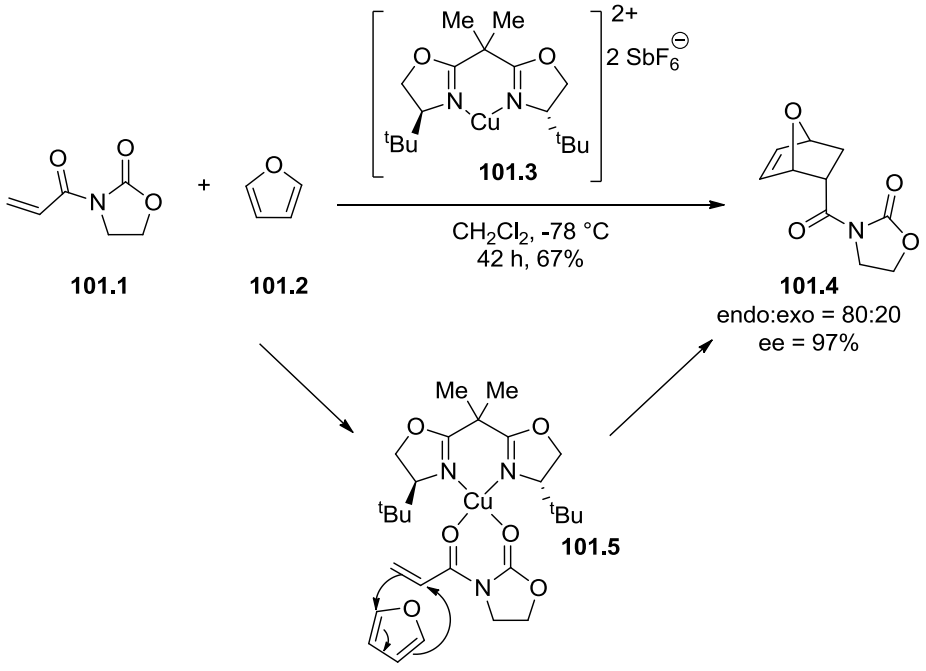
7.3 Hetero-Diels-Alder Chemistry

Since its discovery in 1928, by Otto Diels and his then student Kurt Alder,[248-250] the Diels-Alder reaction has become one of the cornerstone reactions of organic chemistry for the construction of six membered rings.[249] The conventional Diels-Alder reaction is a [4+2] cycloaddition reaction of a conjugated diene **100.1** and a dieneophile **100.2** (usually an electron deficient alkene) to form a cyclohexene ring **100.3** (Scheme 100).



Scheme 100. Diels-Alder reaction

Since its discovery, an understanding of the molecular orbital theory developed by Woodward and Hoffmann,[251] has enabled the Diels-Alde reaction to be used for the asymmetric synthesis of compounds, with reactions often proceeding with excellent levels of region- and stereocontrol.[252-254] A prominent example of this is the use of copper bisoxazoline catalyst **101.3**, for the enantioselective Diels-Alder reaction of acrylimide **101.1** and furan **101.2** to afford cycloadduct **101.4** in 67% yield, which was achieved in 80:20 endo selectivity and 97% ee.[253] It is proposed that the chiral ligand of complex **101.3** is able to create a stereoselective environment around the metal centre, that forces the furan dienophile to approach the diene from "below" the ligand, as shown for transition state **101.5**.



Scheme 101. An enantioselective example of Diels-Alder reaction[253, 254]

A further development in Diels-Alder methodology was replacing the alkene as the dieneophile with a heteroatom containing dieneophile, in what has become known as the hetero-Diels-Alder (HDA) reaction. The HDA reaction is less well investigated than the original Diels-Alder reaction, but its synthetic utility is becoming increasingly recognised.[249, 255] One of the most notable areas where the HDA reaction has been well utilised is for the synthesis of monosaccharides,[233-235, 256-259] which was pioneered by the Danishefsky group, who developed HDA methodology for their synthesis using Danishefsky type dienes, summarised in Figure 22.

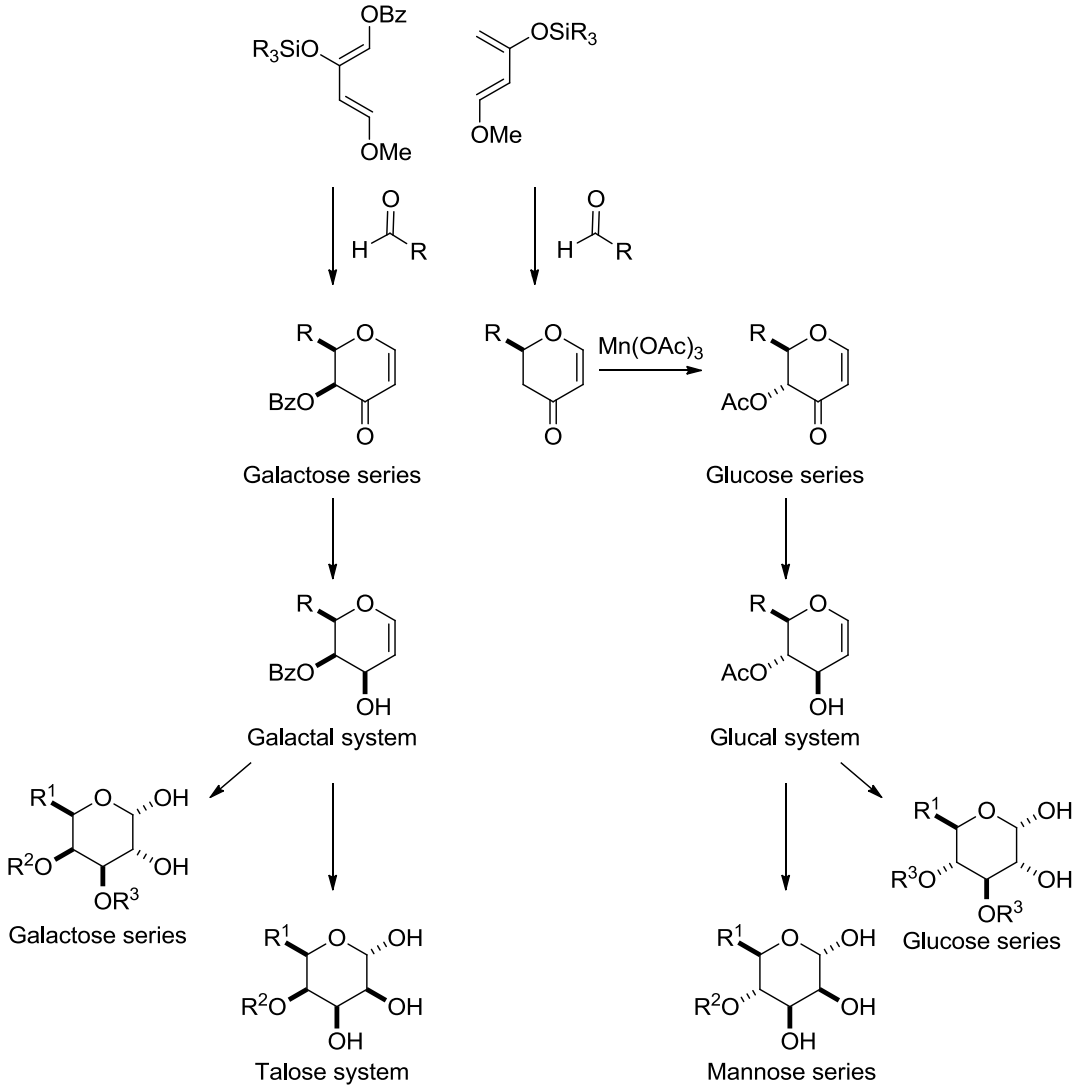
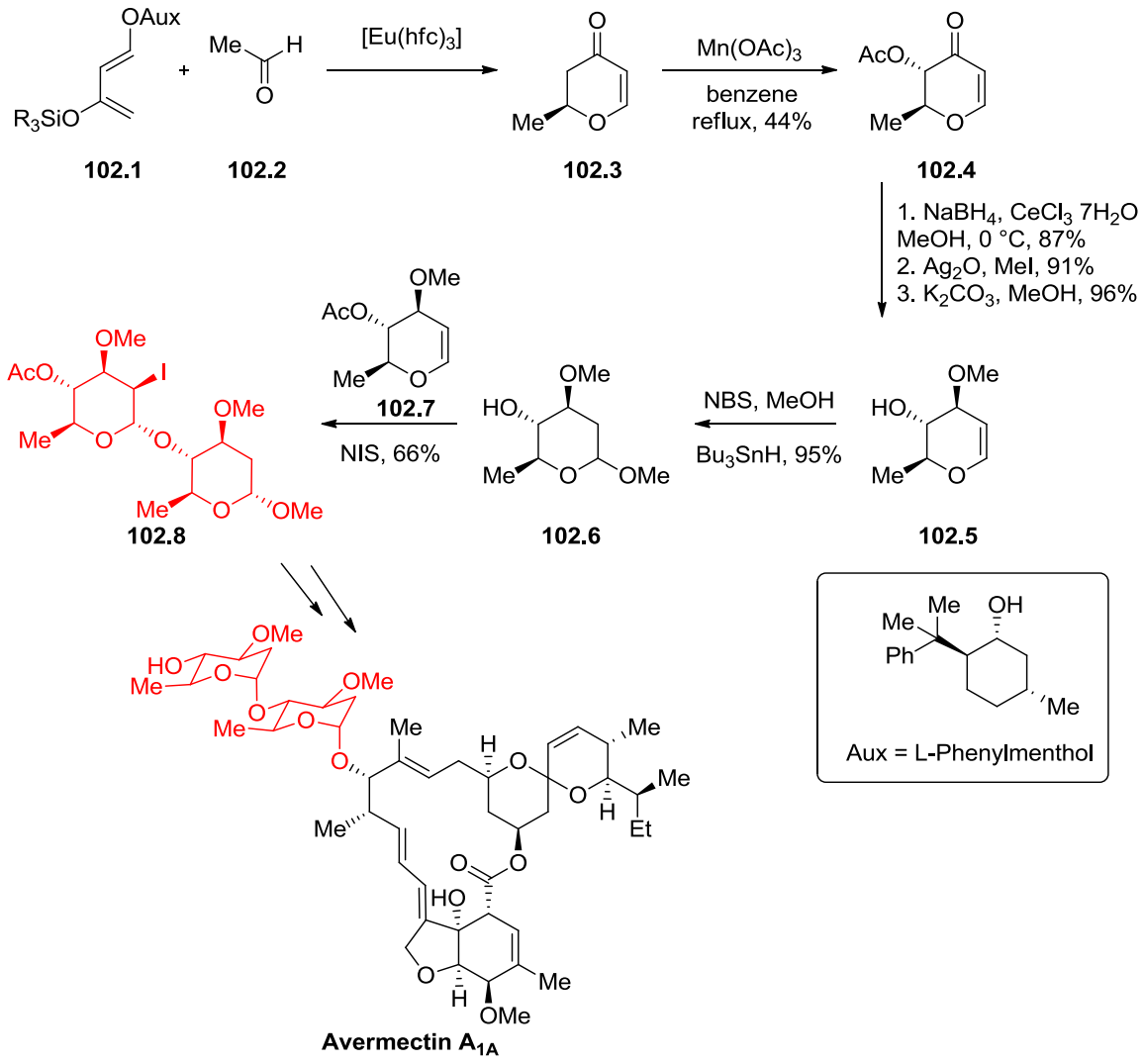


Figure 22. Danishefsky's route to totally synthetic hexoses[234]

An excellent example where this methodology has been applied to natural product synthesis is for the total synthesis of avermectin A_{1A}.[235, 260, 261] A transition metal catalysed HDA

reaction of diene **102.1** (using L-phenylmenthol as a chiral auxiliary to introduce stereocontrol) and acetaldehyde **102.2** afforded the cycloadduct **102.3**, which was oxidised with $Mn(OAc)_3$ to give dihydropyranone **102.4**. Pyranone reduction with sodium borohydride in the presence of $CeCl_3$, afforded a vinyl alcohol that was *O*-methylated followed by acetate hydrolysis to afford alcohol **102.5**. Methoxybromination of **102.5** followed by debromination (using Bu_3SnH) afforded methyl glycoside **102.6**. Reaction of methyl glycoside **102.6** with dihydropyran **102.7** (obtained from **102.4**) with *N*-iodosuccinimide afforded the protected disaccharide **102.8**, that proved to be a crucial fragment for the synthesis of the disaccharide fragment of avermectin A_{1A}.



Scheme 102. Total synthesis of avermectin A_{1A} using HDA chemistry[235, 260, 261]

HDA reactions involving a diene and a carbonyl dienophile proceed with normal electron demand, (HOMO of the diene overlap with LUMO of the dienophile Figure 23), however, hetero atom containing dieneophiles are generally not as reactive as alkenes for Diels-Alder chemistry. To overcome this, Lewis acids (LA) are often required to catalyse the reaction by improving overlap of the HOMO and LUMO orbitals of the respective diene and heterodienophile (Figure 24). The LA coordinates to a lone pair of the hetero atom of the dinenophile acting as an electron withdrawing group to lower the energy of the LUMO orbital. This the energy of the LUMO of the dieneophile closer to the HOMO of the diene allowing for more efficient overlap and cyclisation to occur.

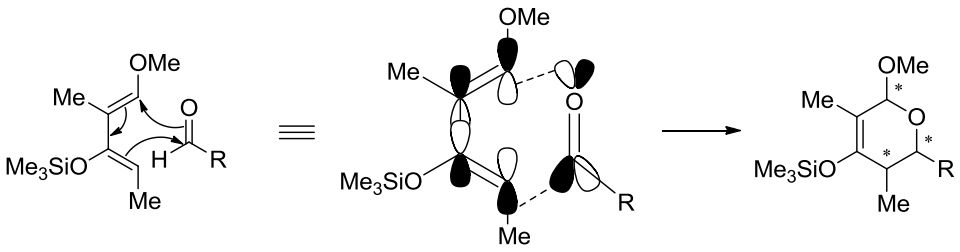


Figure 23. Hetero-Diels-Alder reaction

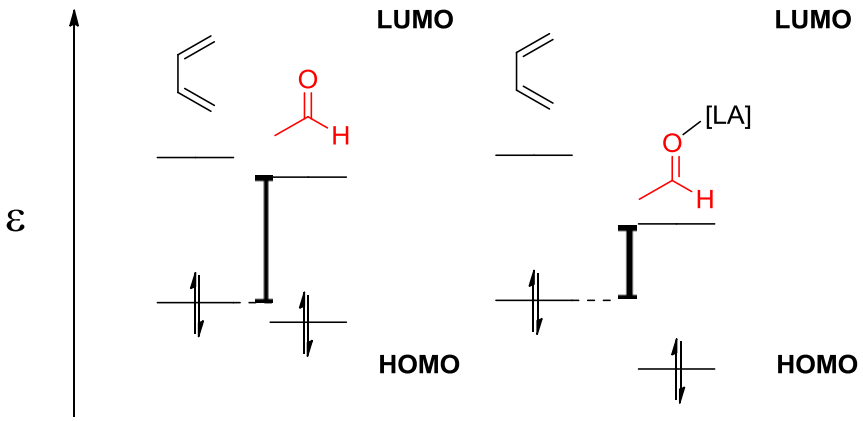
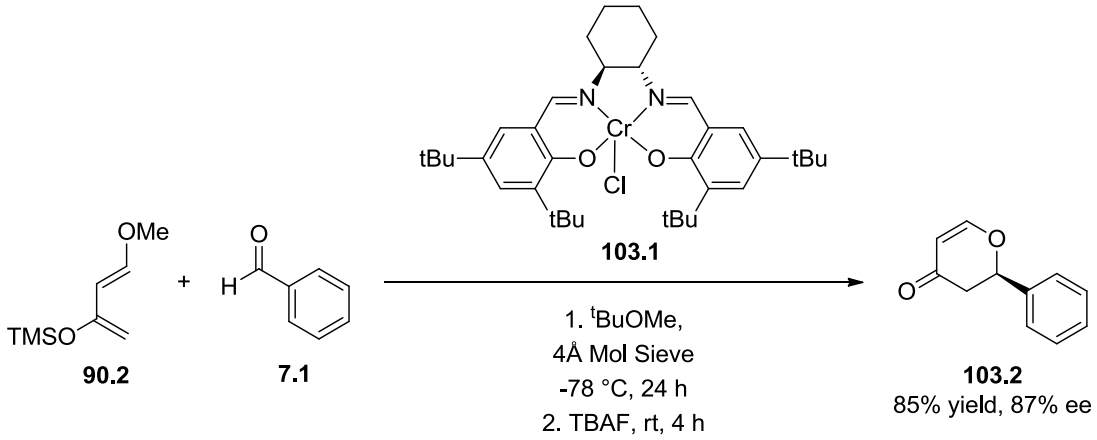


Figure 24. Frontier molecular orbitals of Lewis acid catalysed HDA reaction

The LA may not only act as a catalyst to facilitate the HDA reaction, but also presents an opportunity to confer further control over the reaction, with extensive work having been conducted into using chiral auxiliaries and chiral catalysts for achieving enantio- and diastereoselective control.[249]

7.31 Dihydropyran Synthesis

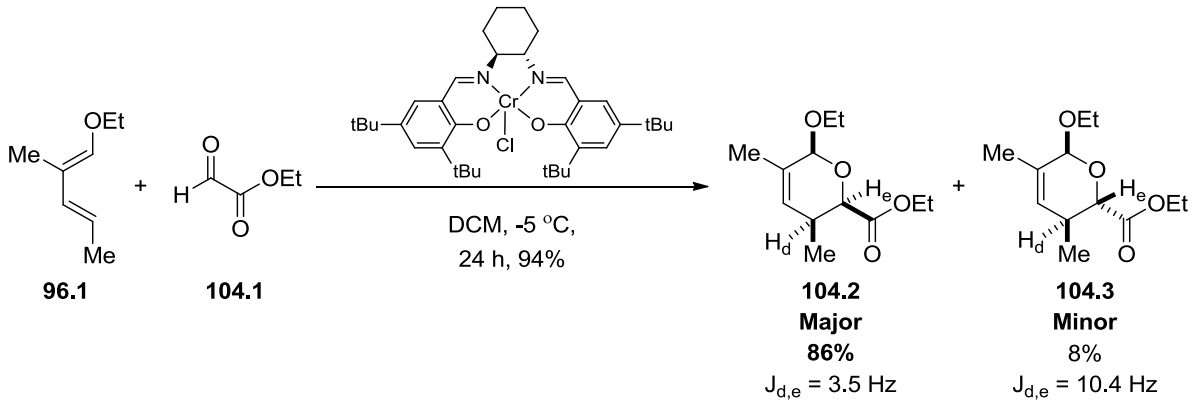
Initial HDA studies were performed with the commercially available Jacobsen bidentate catalyst **103.1**. This catalysts was chosen not only for the convenience of being commercially available, but it has also been shown in literature to be active for a range of asymmetric HDA reactions.[262] It had been reported that HDA reaction between Danishefsky's diene **90.2** and benzaldehyde **7.1** using this catalyst, followed by *O*-silyl cleavage with TBAF (tetra-n-butylammonium fluoride), gave chiral ketone **103.3** in 85% yield and 87% ee (Scheme 103). This reaction was successfully repeated to ensure the integrity of the commercial catalyst, successfully affording α,β-unsaturated ketone **103.2** in 80% yield and 85% ee.



Scheme 103. Literature example of using Jacobsen catalyst for an enantioselective HDA reaction[262]

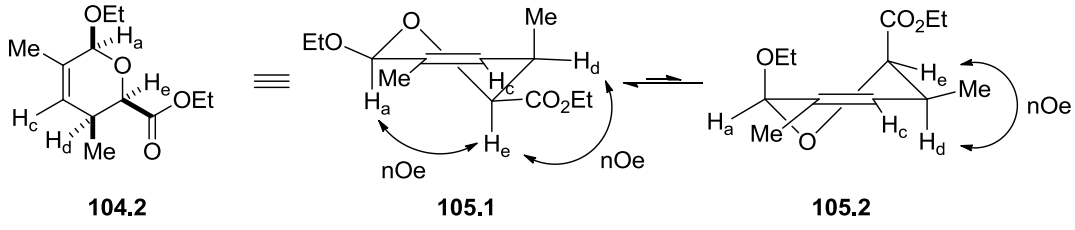
1-Alkoxy dienes are known to be generally deactivated towards cycloaddition reactions,[263] whilst diene **96.1** lacks the activating silyl enol ether fragment of diene **90.1**, so therefore the choice of a reactive carbonyl reaction partner was important. Consequently, the carbonyl substrate chosen for HDA reaction with diene **96.1** was the activated aldehyde ethyl glyoxalate **104.1;** which we proposed would afford a HDA adduct **104.2** that would be ideally suited for further synthetic elaboration.

The reaction proceeded with good diastereoselectivity producing two diastereomers **104.2** and **104.3** in a ratio of 11:1, the two diastereomers, which were separable by column chromatography allowing the single major diastereomer **104.2** to be obtained in 86% yield (Scheme 104).



Scheme 104. Synthesis of dihydropyan **104.2**

The relative stereochemistry of the major diastereomer **104.2** was predicted to be *syn*, due to the *endo* selectivity normally observed for Diels-Alder reactions. However, confirmation was needed, the first piece of evidence was the difference in the coupling constants of Hd and He in the two isolated diastereomers **104.2** (J = 3.5 Hz) and **104.3** (J = 10.4 Hz). A large coupling constant of $J_{d,e}$ = 10.4 Hz for dihydropyran **104.3** is characteristic of an axial-axial relationship, which would require both groups to be *anti* to each other. A small coupling constant on the other hand, such as $J_{d,e}$ = 3.5 Hz for dihydropyran **104.2** is characteristic of a axial-equatorial relationship that would be expected if the protons had a *syn*-relationship. Another way of obtaining evidence of relative stereochemistry is through nOe (nuclear Overhauser effect) NMR experiments. If, as expected, the three protons H_a, H_d and H_e of the major diastereomer had a syn geometry, then nOe interactions would be expected between them, as represented for the major ring conformer shown in Scheme 105. Since nOe interactions occur by through space interactions between protons, these interactions would only be possible if the protons of the dihydropyran ring were on the same face (Figure 26). The use of coupling constants can also help assign relative stereochemistry.



Scheme 105. Dihydropyran **104.2** ring conformation

In order to determine the relative stereochemistry by nOe NMR it is necessary that ^{1}H NMR of the compound in question is fully assigned. The full assignment of dihydropyran **104.2** is presented below (Figure 25). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 - 5.68 (m, 1H, H_c), 5.09 (s, 1H, H_a), 4.34 (d, *J* = 3.5 Hz, 1H, H_e), 4.28 - 4.22 (m, 2H, CH_2^1), 3.87 (dq, *J* = 9.6, 7.0 Hz, 1H, H_g), 3.66 (dq, *J* = 9.5, 7.1 Hz, 1H, H_f), 2.48 - 2.42 (m, 1H, H_d), 1.66 (s, 3H, Me^1), 1.30 (t, *J* = 7.1 Hz, 3H, Me^3), 1.25 (t, *J* = 7.1 Hz, 3H, Me^4), 1.01 (d, *J* = 6.9 Hz, 3H, Me^2). Due to restricted rotation, the acetal ethoxy protons Hf and Hg of dihydropyran **104.2** are diastereotopic. This is confirmed by analysis of the NOESY spectrum which reveals an interaction between Ha and Hg. Once full assignment has been made then inspection of the nOe spectrum allows the relative stereochemistry to be assigned.

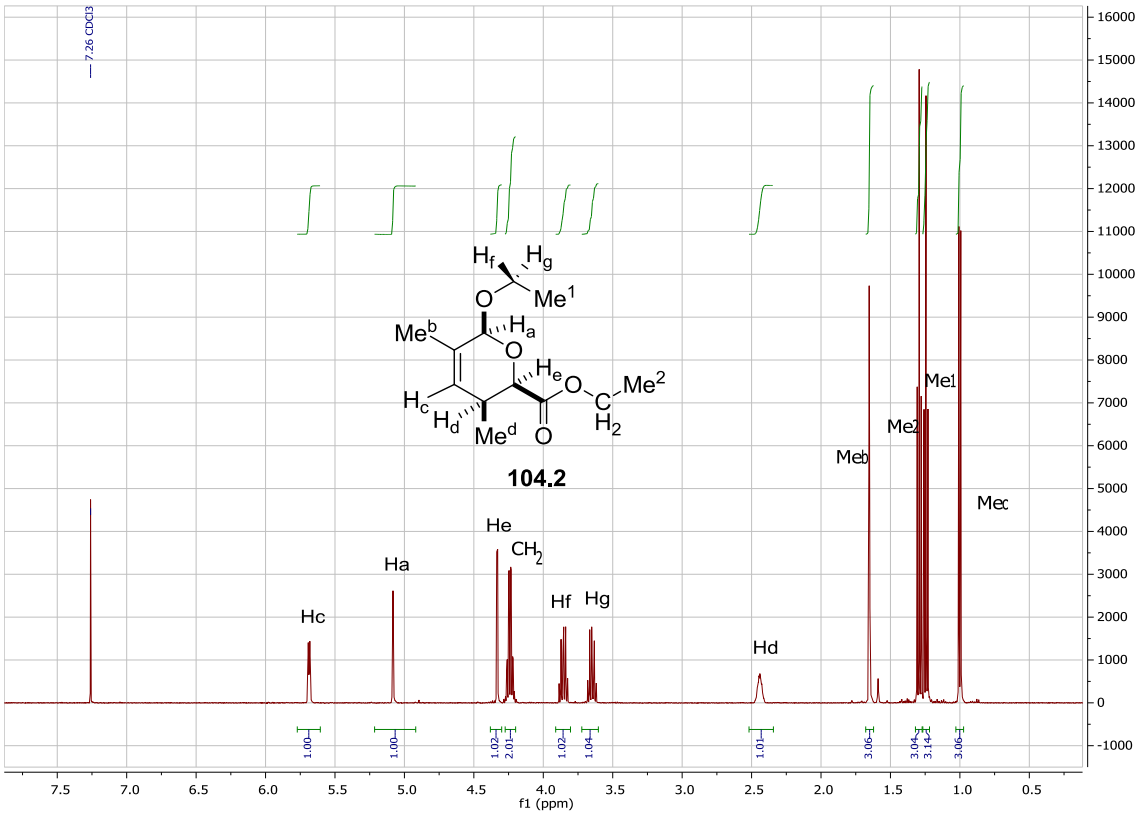


Figure 25. Assaingment of ^{1}H NMR of dihydropyran **104.1**

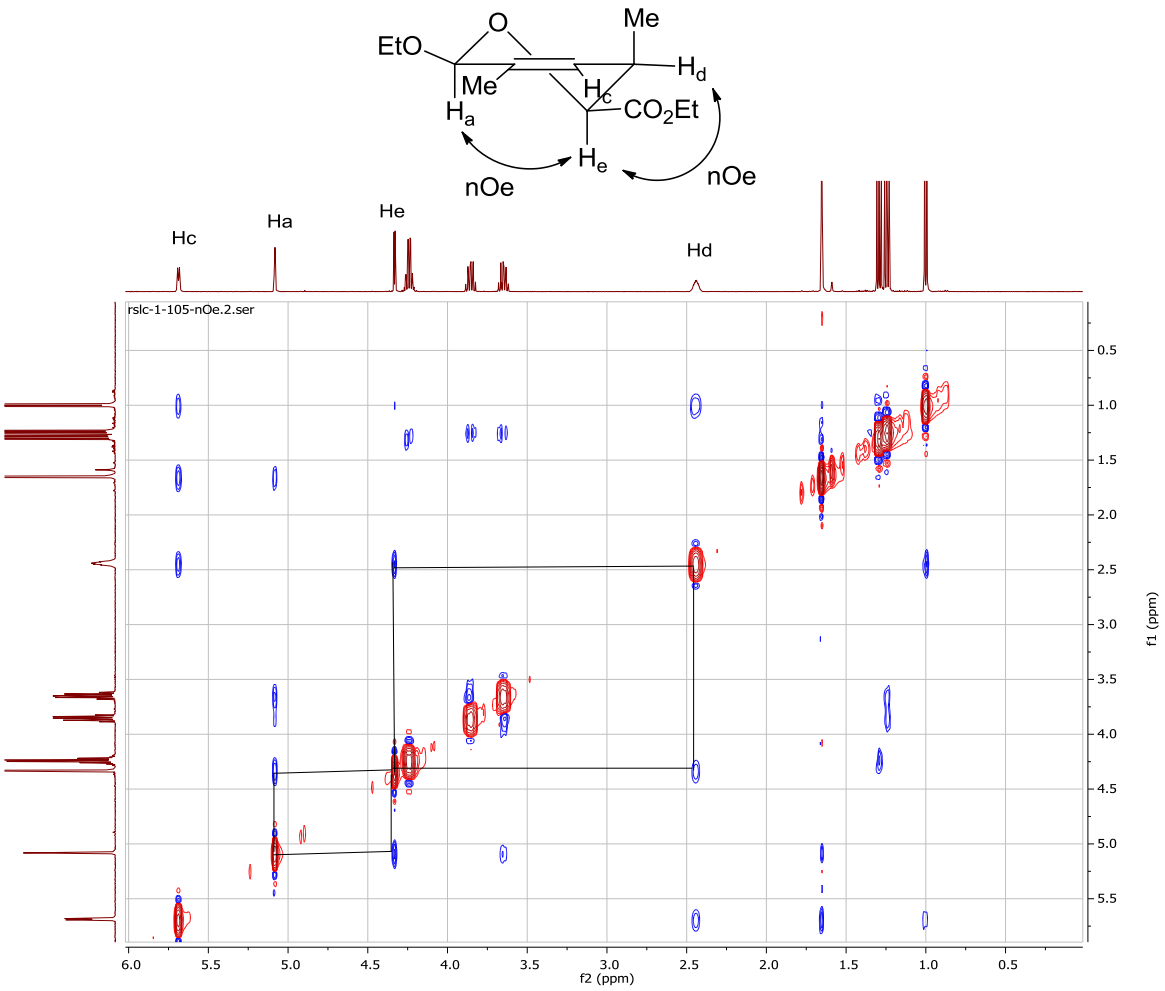
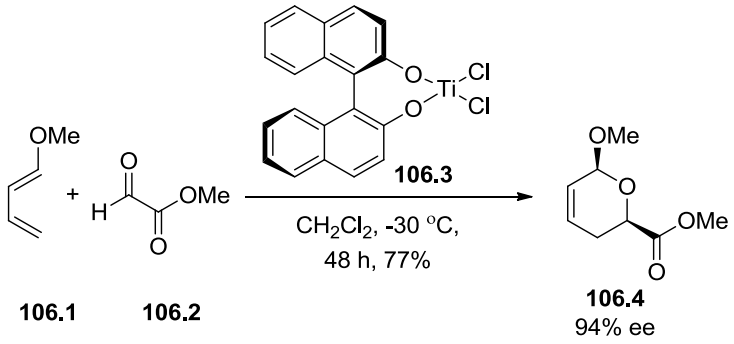


Figure 26. NOESY NMR of dihydropyran **104.2**

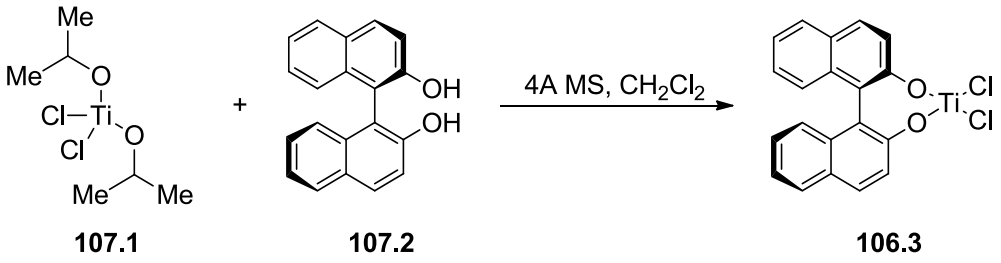
With the relative stereochemistry of dihydropyran **104.2** confirmed the enantiopurity was then determined. A genuine racemic sample of **104.2** was prepared using a racemic sample of catalyst **103.1**. Enantiomeric excess was then determined using chiral GC, using a β-Dex column as the stationary phase. Unfortunately, the enantiomeric excess measured was found to be low at only 15% ee. In an attempt to improve this ee a number of changes were made to the reaction conditions, with an ultimately important modification being prior purification of ethyl glyoxalate **104.1**. Ethyl glyoxalate **104.1** is commercially available as 50% solution in toluene. However, the glyoxalate is commercially available predominantly as its polymeric hydrate, rather than its aldehyde form. Consequently the glyoxalate was distilled/cracked under nitrogen and stored as a 50% solution in anhydrous CH_2Cl_2 at -20 °C to ensure it was present as its reactive aldehyde form. However, this change in this instance (and numerous other modifications), gave no improvement in ee.

These results were highly disappointing, and with the critical need to improve ee of the HDA reaction it was decided to investigate a different chiral catalyst. A catalytic system that had been used on a paramount, similar system was titanium-BINOL **106.3**,[242] which had been reported to catalyse the reaction of diene **106.1** and methyl glyoxalate **106.2**, to afford the cycloadduct **106.4** in 77% yield and 94% ee.



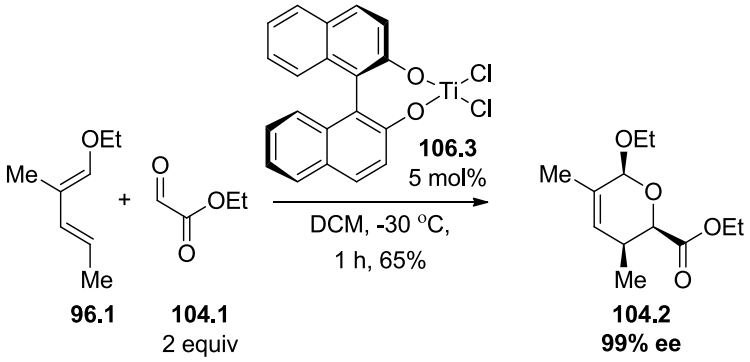
Scheme 106. Mikami *et al.* HDA reaction using Ti-BINOL **106.3**[242]

Catalyst **106.3** was synthesised by addition of diisopropoxytitanium dichloride **107.1** to a stirred mixture of BINOL **107.2** and 4 Å molecular sieves in anhydrous CH_2Cl_2. The reaction was stirred for 1 h and the molecular sieves allowed to settle overnight. The solution was then decanted from the molecular sieves utilizing Schlenk techniques, concentrated and the resultant residue was suspended in anhydrous pentane. The pentane was then removed *via* syringe and the residue dried under vacuum to give the titanium-BINOL complex **106.3**, which was stored under an inert atmosphere and used without further purification (Scheme 107).[242] Complete removal of the molecular sieves was shown in the original paper to be essential to achieve good enantioselective control over the reaction.



Scheme 107. Synthesis of titanium-BINOL catalyst **106.3**

This new catalyst was then applied to the HDA reaction of diene **96.1** and purified ethyl glyoxalate **104.1**, pleasingly this change had the desired effect, with very high enantioselectivity achieved of 99% ee. A small optimization study was carried out, which identified that use of diene **96.1** as the limiting reagent, resulted in the reaction proceeding to **104.2** as a single diastereomer in 65% yield and most importantly, in 99% ee (Scheme 108).



Scheme 108. Enantioselective synthesis of dihydropyran **104.2**

Enantioselective induction from the BINOL ligand is believed to result from binding of the when the Ti-BINOL complex to glyoxalate to create a highly chiral environment around the aldehyde. This only allows the diene to approach from one face of the aldehyde, resulting in formation of both a single diastereomer and a single enantiomer (Figure 27).

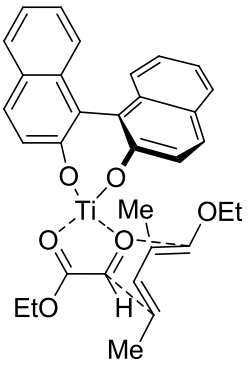


Figure 27. Ti-Binol-glyoxalate transition state for the enantioselective synthesis of dihydropyran **104.2**.

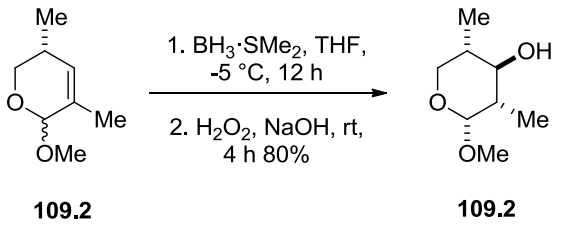
However, while this was an important step forward in validating this HDA project, it was found that different batches of Ti-BINOL **106.3** resulted in widely different ee's of dihydropyran **104.2**, ranging from 99% to 0% ee! In order to address this issue of reproducibility it was decided to subsequently synthesise Ti-BINOL catalyst **106.3** in a glove box to ensure the quality of the catalyst produced. This change was made under the assumption that the reaction and performance of the catalyst were highly sensitive to the presence of adventitious water. Pleasingly, this change in synthetic procedure rectified the reproducibility issue associated with using catalyst **106.3** in our HDA reaction, enabling access to gram quantities of enantiomerically enriched dihydropyran **104.2**. Consequently our attention then switched to employing **104.2** as a chiral template for carrying out a series of diastereoselective derivatisation reactions to afford a library of chiral building blocks.

7.4 Dihydropyran Derivatization

It was proposed that subsequent reactions performed on the dihydropyran ring should proceed with a high level of diastereoselectivity due to its cyclic conformation, which ideally would mean that chiral reagents would not be necessary, with all the stereocontrol ultimately being controlled by the original enantioselective HDA reaction.

7.41 Hydroboration

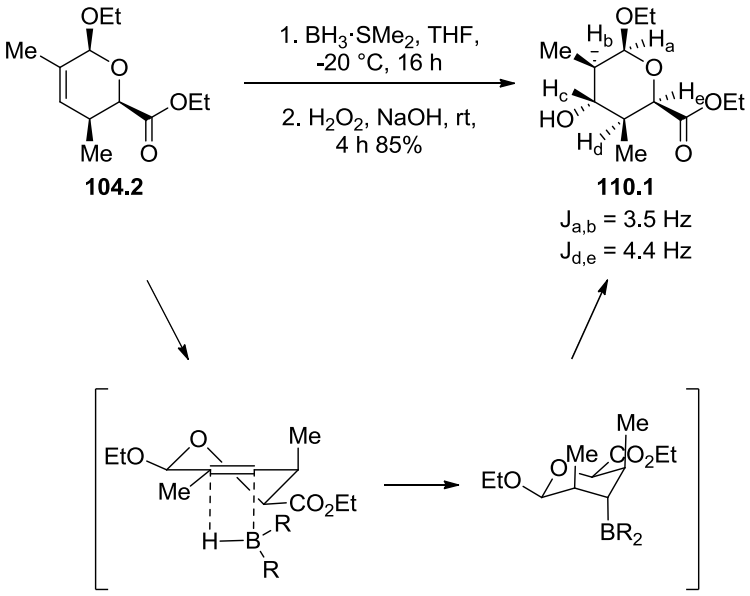
The first reaction considered was hydroboration of the alkene functionality of **104.2**; which would lead to the introduction of the desired hydroxyl group and the generation of two new stereocentres. There are a number of similar literature examples that suggested that this hydroboration reaction would occur with good facial selectivity. In particular, the seminal work of Danishefsky has demonstrated that good selectivity could be achieved for hydroboration reactions of dihydropyran **109.2**, using simple hydroborating reagents such as borane (Scheme 109).[237]



109.2 **109.2**

Scheme 109. Stereoselective hydroboration reaction of dihydropyran **109.2**[237]

The hydroboration reaction of dihydropyran **104.2** proved to be successful and proceeded with good selectivity, affording a single diastereomer in 85% yield (Scheme 110).



Scheme 110. Stereoselective hydroboration of dihydropyran **104.2**

The borane approaches the alkene *via* its least hindered face and undergoes *anti*-Markovnikov addition, which upon oxidative workup affords pyran **110.1**, whose hydroxyl group has a *anti* relationship relative to the other substituents, with the relative stereochemistry again being confirmed by NOESY NMR spectroscopic studies. Key nOe interactions between H_a, H_b, Hd and H_e confirm that all four protons are on the same face of the pyran ring, with H_c not interacting with any of the other pyran protons other than H_d due to their vicinal equatorial relationship (Figure 28).

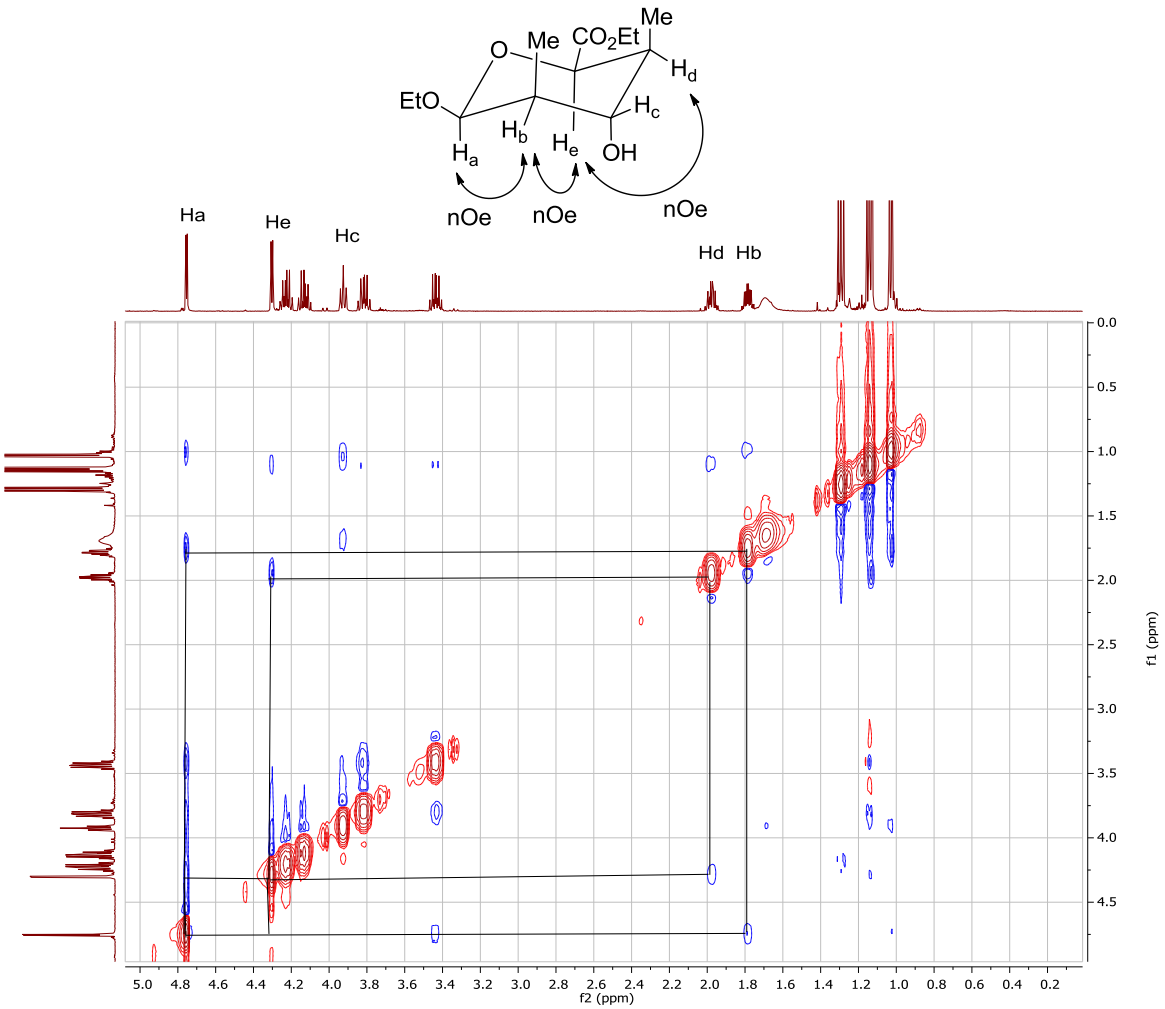


Figure 28. NOESY NMR of pyran **110.1**

The incorporation of a hydroxyl group not only creates two new stereocentres, but also gives the potential for further derivatization reactions towards the synthesis of a wide range of natural products, potentially making it a highly valuable building block. Hydroboration also results in the generation of a stereotetrad, which as mentioned previously is a highly common structural motif in polyketide natural products.[169] For example, the diastereomer of pyran **110.1** produced is stereochemically equivalent to the stereotetrad containing a *syn, syn, syn* relative stereochemistry, which is present in polyketide natural products such as Erythromycin A (Figure 29).

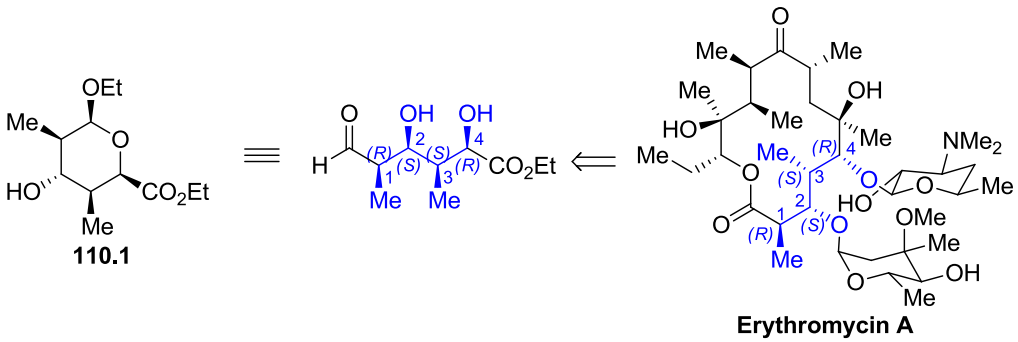
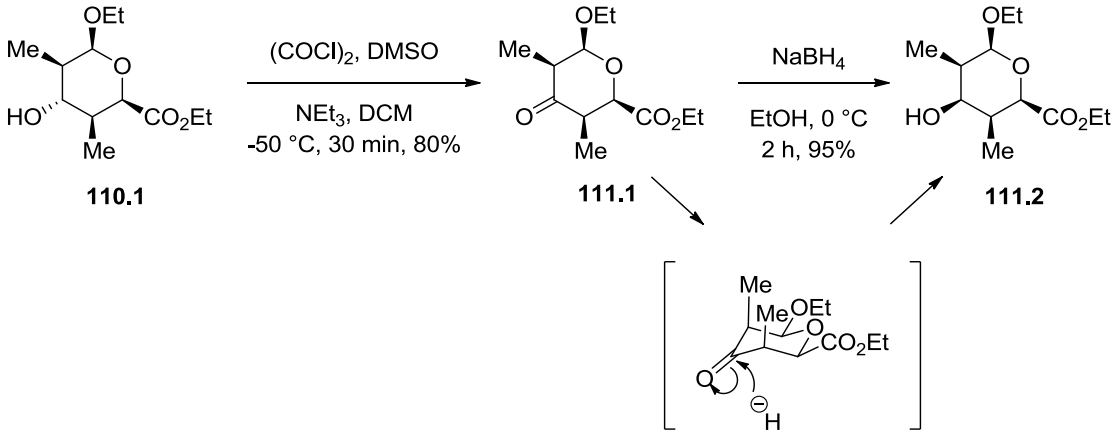


Figure 29. Erythromycin A.

7.411 Hydroxyl Inversion

However, in order to gain complementary access to another diastereomeric tetrad it was decided to oxidise the hydroxyl group of **110.1** and then subsequently reduce the resulting ketone to afford an inverted hydroxyl functionality. The success of this method would rely on the inverted hydroxyl group product being produced *via* attack of the hydride from the least hindered face of the ketone functionality of pyranone **111.1**. Therefore, alcohol **110.1** was oxidised to ketone **111.1** under Swern conditions, with the reaction proceeding well to afford pyranone **111.1** in 80% isolated yield. The ketone reduction was performed with sodium borohydride in ethanol at 0 °C to give the inverted alcohol **111.2** in a 95% yield (Scheme 111). Pleasingly, this reduction reaction proceeded to give a single diastereomer, confirming that pyran **111.2** could be successfully accessed as a sole diastereomer under kinetic control. Access to ketone **111.1** potentially presents an opportunity for carrying out other derivatisation reactions, *via* treatment with different nucleophiles to afford a range of natural and non-natural synthons.



Scheme 111. Inversion of hydroxyl group on pyran **110.1**

The relative stereochemistry of pyran **111.2** was again confirmed by nOe NMR spectroscopic studies, with key nOe interactions between H_a, H_b, H_c, H_d and He confirming that they are all present the same face of the pyran ring, and therefore have and all *syn*-relationship (Figure 30).

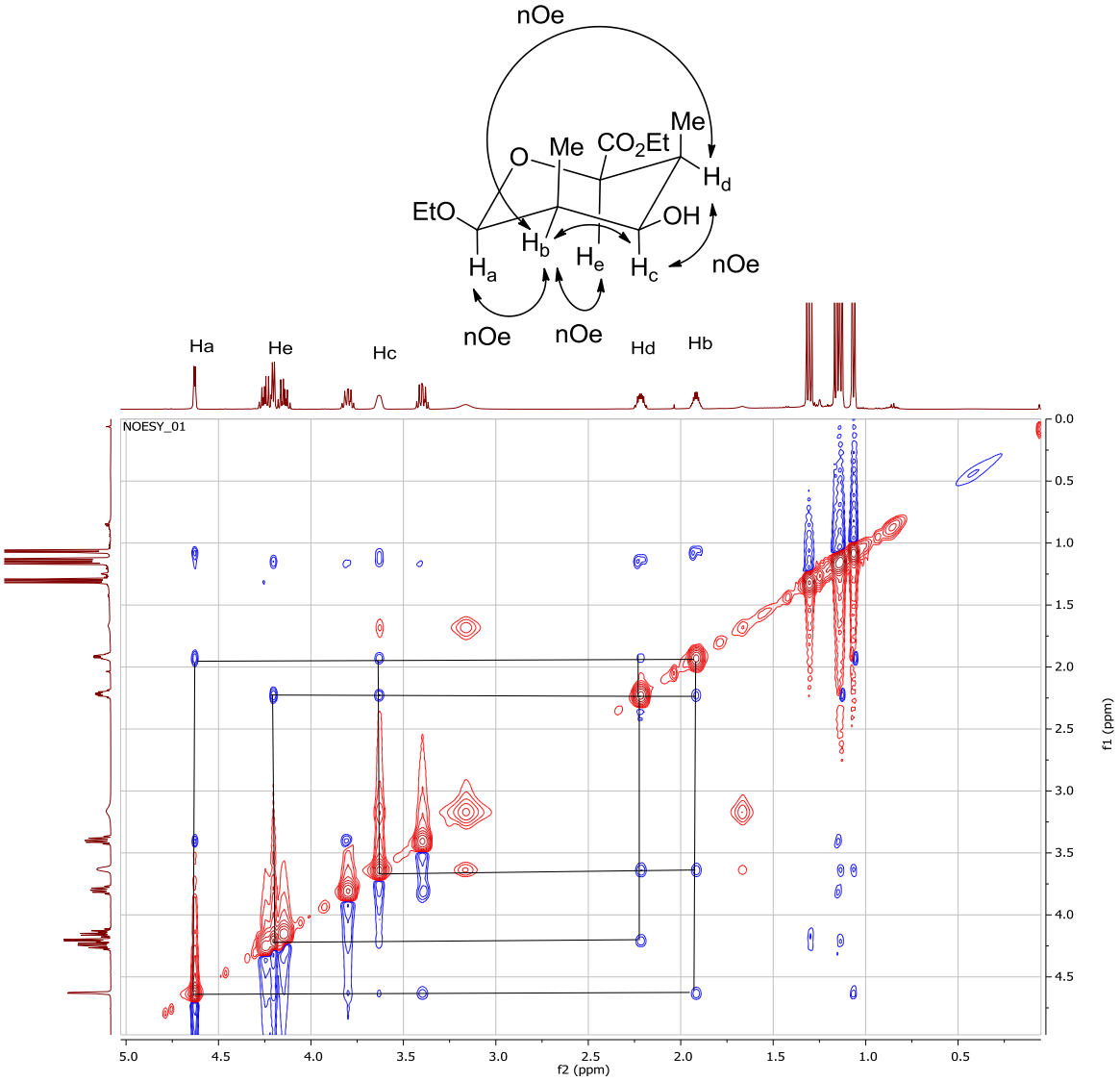


Figure 30. NOESY Spectra of pyran **111.2**

The tetrad stereochemistry of pyran **111.2** produced is equivalent to the *anti, anti, syn* relative stereochemistry, which is found as a pair of enantiomeric fragments present in the natural product Aplyronine A (one of each enantiomer) (Figure 31).

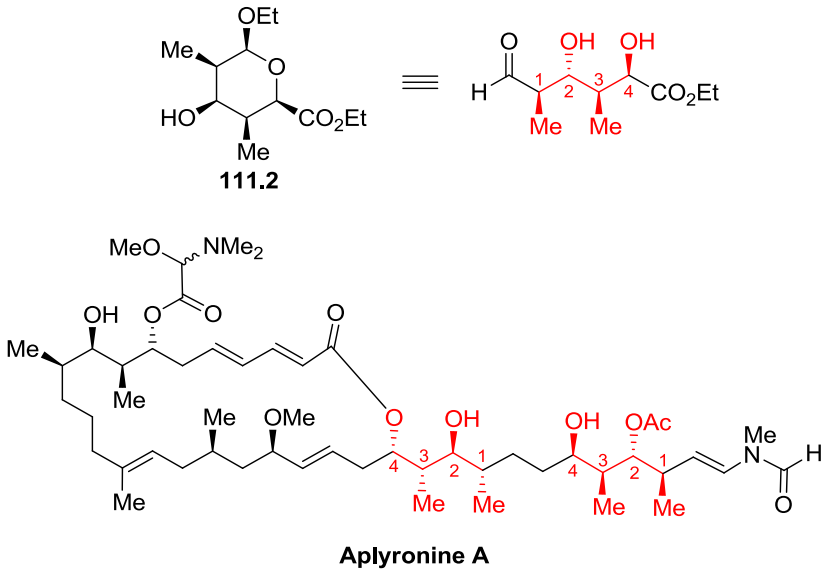
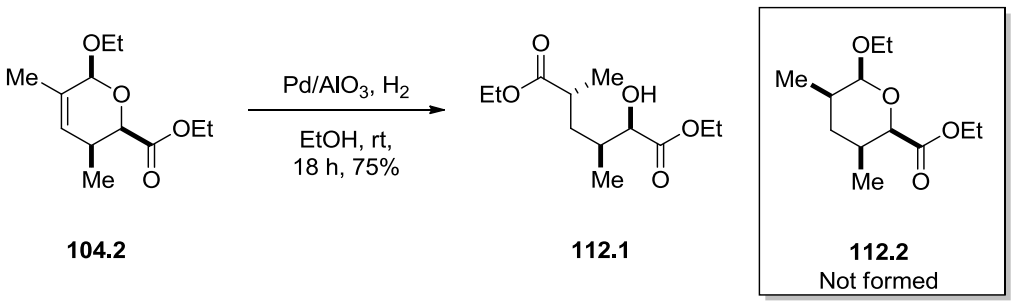


Figure 31. Aplyronine A

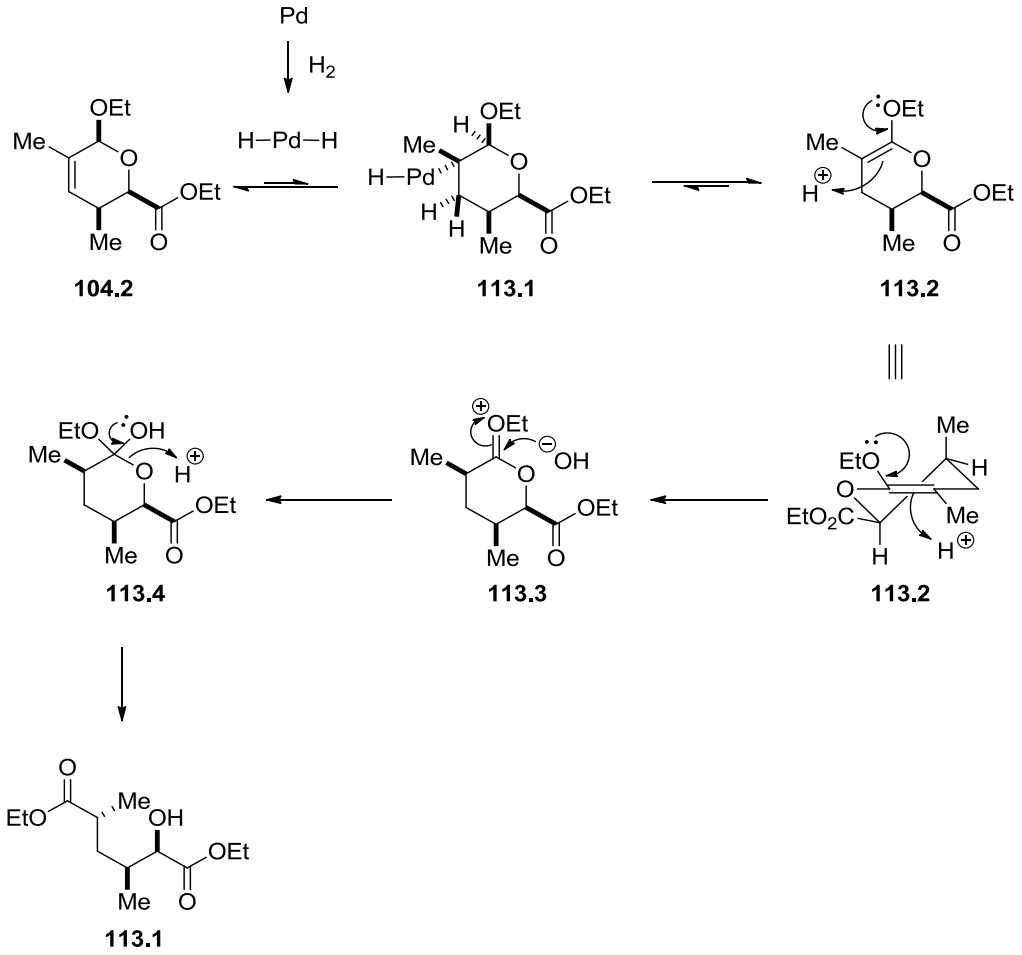
7.42 Hydrogenation

We next targeted another derivatization reaction of dihydropyran **104.2** involving hydrogenation of the alkene functionality. This transformation was expected to proceed with good stereoselectively, due to the mechanism of hydrogenation reaction; whereby the alkene substrate is adsorbed onto the heterogeneous metal catalyst surface, followed by *syn* addition of hydrogen across the double bond. However, initial hydrogenation attempts proved to be unsuccessful, instead unexpectedly affording acyclic bis-ester **112.1** as the sole product from the reaction (Scheme 112).



Scheme 112. Hydrogenation of **104.2** affording bis-ester **112.1**

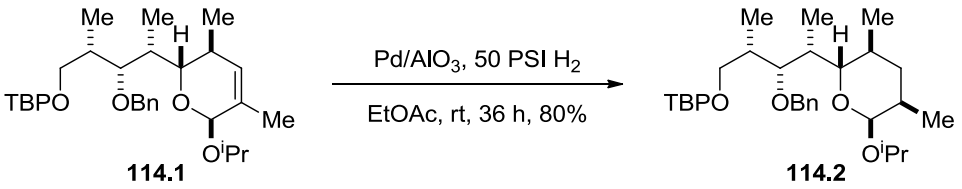
A proposed mechanism for this unexpected transformation is shown below in Scheme 113. Pd-H addition across the alkene bond of dihydropyran **104.2** affords a *syn* adduct **113.1**. However, at low pressures of hydrogen, this process is reversible, enabling competing elimination of the Ha proton to afford alkene **113.2**. Stereoselective protonation of the enol ether fragment of **113.1** affords an oxacarbenium species **113.3**, which is then hydrolysed to give bis-ester **112.1** (Scheme 113).



Scheme 113. Proposed mechanism for the formation of bis-ester **112.1**

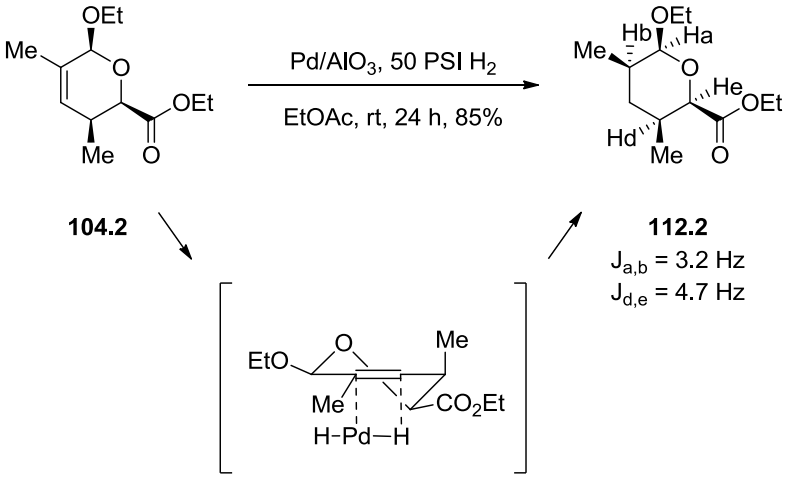
As a consequence of this unexpected reaction, it was decided to perform the hydrogenation reaction in an aprotic solvent under a high pressure of Hydrogen, since a related literature example by the Danishefsky group suggested this might be successful.[237, 241] It was reported that when alkene **114.1** was subjected to a H_2 atmosphere of 50 PSI in the presence of

a palladium on alumina catalysts, it afforded the fully saturated pyran **114.2** in 80% yield (Scheme 114).



Scheme 114. Literature hydrogenation example[237]

Under these conditions, the hydrogenation of dihydropyran **104.2** with palladium on alumina under an atmosphere of 50 PSI hydrogen for 24 h afforded tetrahydropyran **112.2** as a single diastereomer in 85% yield (Scheme 115).



Scheme 115. Synthesis of pyran **112.2**

The relative stereochemistry of pyran **112.2** was once again confirmed by nOe interactions. The key nOe interactions that confirm the assignment of the configuration of the methyl group, are that of H_b which is shown to interact with both H_a and H_e confirming the relative stereochemistry of pyran **112.2** (Figure 32). Pyran **112.2** has been previously synthesised by the Evans group as its enantiomer,[264] with a comparison of the analytical data confirming the

structure of pyran **112.2**, as well as a comparison of the optical purity ($[\alpha]_D^{20}$ = +82, literature $[\alpha]_D^{20}$ -88 for opposite enantiomer[264]).

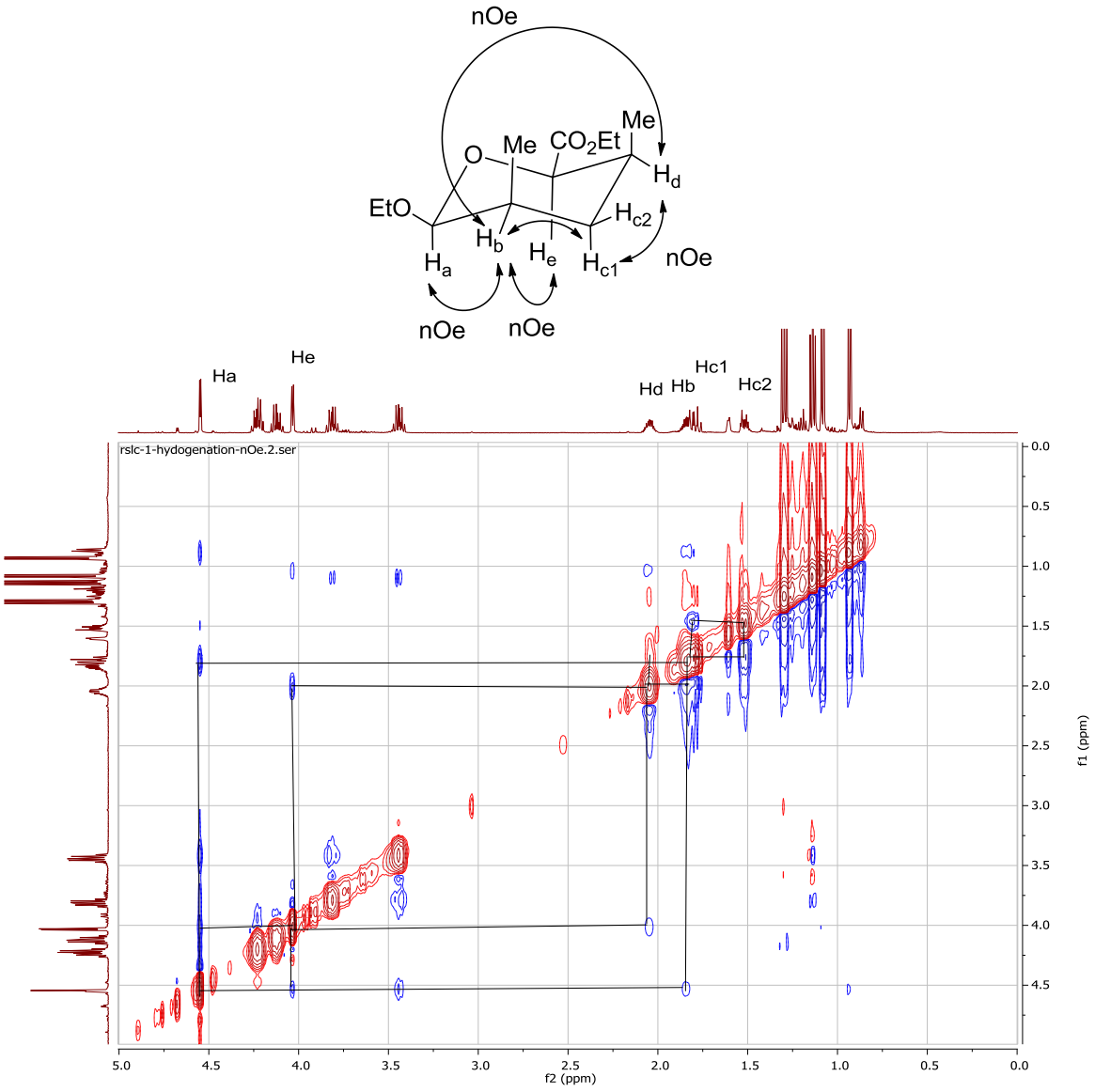


Figure 32. NOESY NMR of pyran **112.1**

Pyran **112.2** contains a polydeoxypropionate fragment which is also present in many natural products, with a tetrad fragment with the same relative configuration being present in the natural product bourgeanic acid (Figure 33).[265]

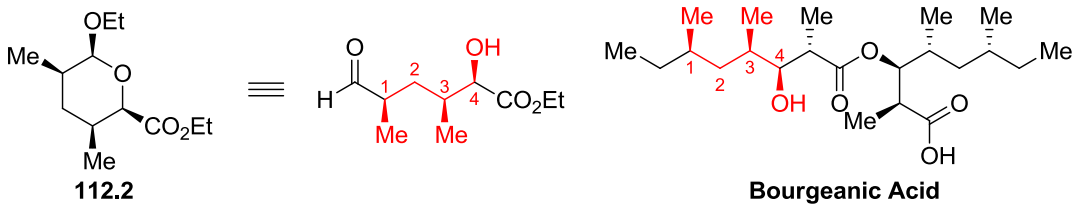
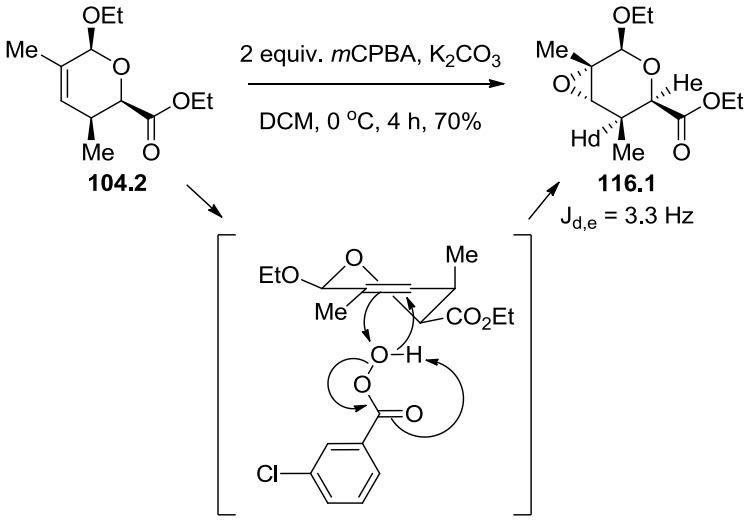


Figure 33. Bourgeanic acid

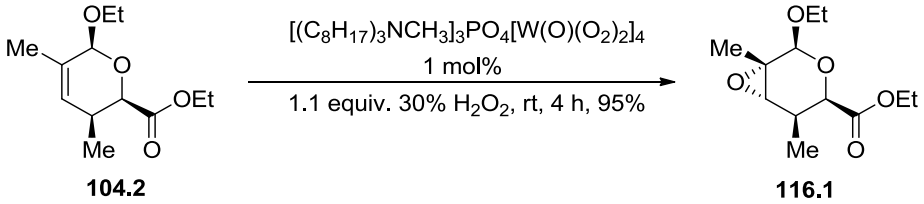
7.43 Epoxidation

Epoxidation of alkenes is an important reaction in synthetic chemistry not only for generation of epoxides, but also for their synthetic capacity to introduce further functionality into a molecule. One of the most utilized methods of epoxidation is through the use of *m*-chloroperbenzoic acid (*m*CPBA). Initial attempts to epoxidise dihydropyran **104.2** were made using *m*CPBA, with the reaction proceeding well at 0 °C in four hours, using potassium carbonate as a buffer to prevent the chlorobenzoic acid by-product from ring the opening epoxide **116.1** product (Scheme 116). The relative stereochemistry of the resultant epoxide **116.1** can be explained due to the mCPBA approaching the double bond from the least hindered face. However, this methodology proved unreliable, with yields varying considerably when the reaction was repeated on scale, and with isolation of epoxide **116.1** proving problematic.



Scheme 116. Epoxidation of dihydropyran **104.2** using mCPBA

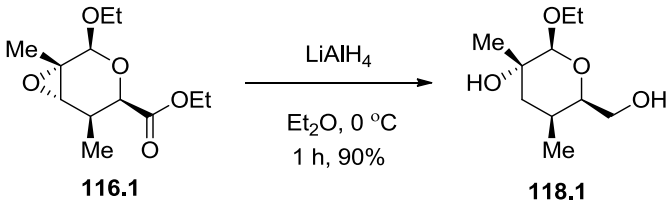
Due to these issues it was decided to try and identify an alternative epoxidation method for trisubstituted alkenes. An example that came to our attention was the methodology described by Venturello and Noyori,[266, 267] who have both published excellent methods employing H_2O_2 and *in situ*-generated, or preformed metal complexes. The most commonly employed catalyst is a tungstate complex, composed of quaternary ammonium tetrakis(diperoxotungsto)phosphates (-3), which not only acts as the epoxidation catalyst, but also acts as a phase transfer catalyst. The reaction utilises H_2O_2 as the oxidant, which is one of the greenest oxidants available, producing water as a by-product. The method chosen to follow was using a preformed tungstate complex as described by Venturello,[266] which was prepared by heating tungstic acid in 30% H_2O_2 at 60 °C until the reaction becomes homogeneous. The reaction was then cooled to rt and 40% phosphoric acid solution added, and the reaction diluted with H_2O followed by the addition of Aliquat 336. Aqueous work-up followed by concentration *en vacuo* then provided the desired tungstate complex. The epoxidation reaction of dihydropyran **104.2** proceeded in excellent yield at rt in 4 h, under solvent free conditions, to give epoxide **116.1** in a 95% yield as a single diastereomer (Scheme 117). The reaction was demonstrated to have excellent reproducibility, and was a significant improvement on the original *m*CPBA epoxidation conditions.



104.2 **116.1**

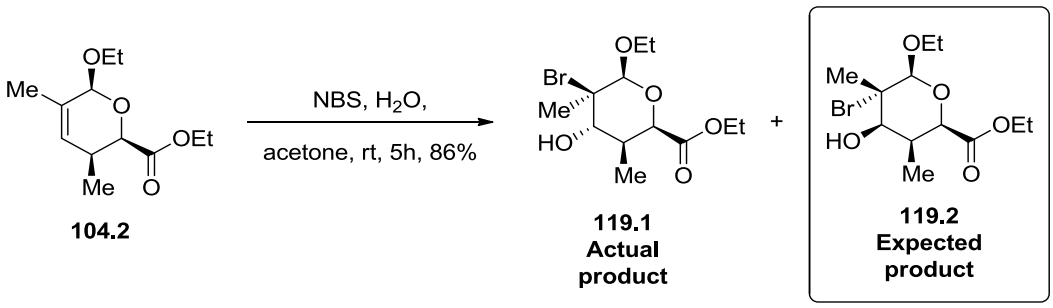
Scheme 117. Venturello catalyst epoxidation of dihydropyran **104.2**

Reduction of epoxide **116.1** with $LiAlH_4$ proceeded well to give the expected Markovnikov tertiary alcohol **118.1** in 90% yield after 1 h, with the ester functionality also being reduced to a primary alcohol to afford diol **118.1** (Scheme 118), containing orthogonally addressable groups for further derivatization. This reduction reaction proceeds *via* an S_N2 type mechanism, because the reaction in performed in a polar aprotic solvent, which results in the hydride nucleophile approaching the epoxide with an axial trajectory at the least hindered carbon.



Scheme 118. Reduction of epoxide **30.1** with $LiAlH_4$

Attempts were also made to access the opposite diastereomer of epoxide **116.1** through base mediated ring-closure of bromohydrin **119.1**. Dihydropyran **104.2** was subjected to standard bromohydrin synthesis conditions utilising *N*-bromosuccinimide (NBS) and water. However, rather than producing the expected bromohydrin **119.1** *via* approach of NBS from the least hindered face, it was found that bromohydrin **119.2** was generated as the only product in 86% yield (Scheme 119). Fortunately, the bromohydrin produced could be isolated as a crystalline solid which allowed for confirmation of its structure by single crystal X-ray crystallography (Figure 34).



Scheme 119. Synthesis of bromohydrin **119.1**

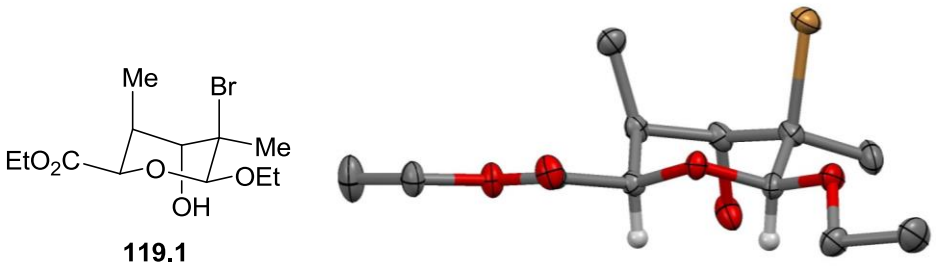
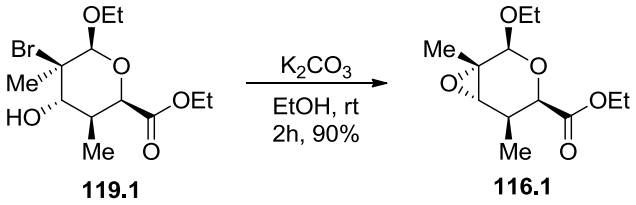


Figure 34. X-ray crystal structure of bromohydrin **119.1** (hydrogens omitted for clarity)

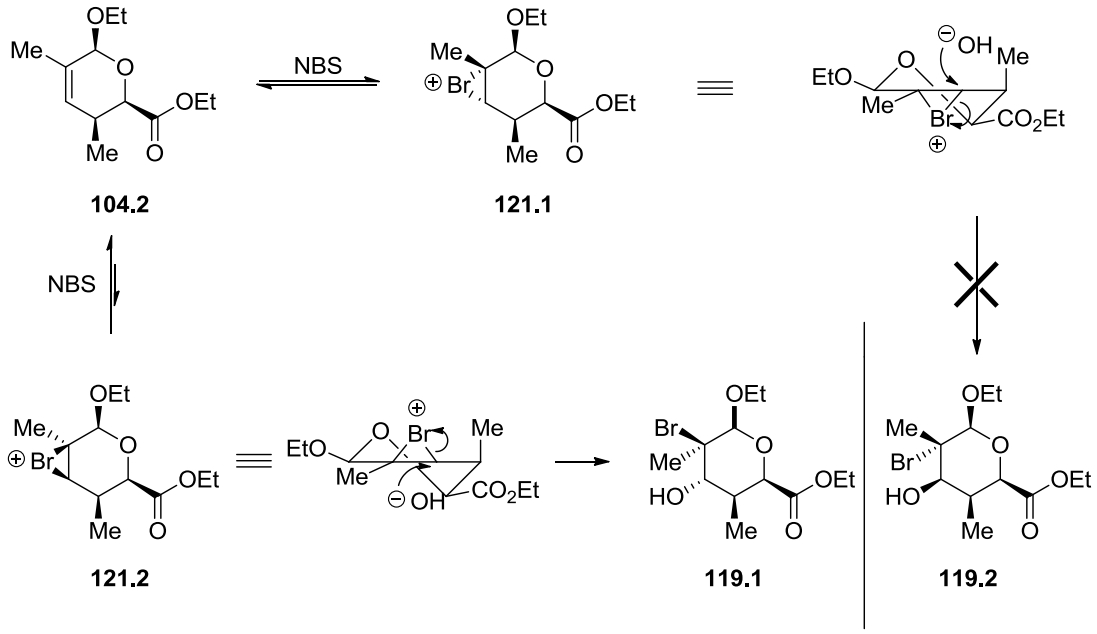
As confirmation that the epoxide generated using the Venturello conditions had been assigned correctly, bromohydrin **119.1** was cyclised using potassium carbonate as base to afford epoxide **116.1** in 90% yield (Scheme 120). Comparison of the ^{1}H NMR and ^{13}C NMR spectra of both synthesised epoxides and a mixed NMR sample provided confirmation that both routes had led to generation of the same epoxide diastereomer **116.1**.



Scheme 120. Ring closing to form epoxide **116.1**

This unexpected bromohydrin result is proposed to be due to two contributing factors. Firstly, electrophilic bromination of an alkene double bond is known to proceed *via* reversible formation of a bromonium ion.[268-271] Secondly, the trans-diaxial effect (Fürst-Plattner rule),[272] states that nucleophilic attack of cyclohexyl derivatives such as epoxides, imines and halonium ions occurs to preferentially afford trans-diaxial product.[272, 273]

If formation of bromohydrin **119.2** is considered, the bromonium ion would be expected to arise from approach of Br^{+} from the least hindered face, resulting in formation of bromonium ion **121.1**. If this is considered as a "bow-tie" conformation, then hydroxyl attack of the bromonium ion to produce a trans-diaxial product would proceed *via* a highly disfavoured "twist boat" conformation. However, since bromonium ion formation is potentially reversible, small quantities of the more sterically hindered bromonium ion **121.2** may also be formed. Hydroxyl attack of bromonium ion **121.2** could then proceed smoothly to give the "chair" conformation of the bromohydrin, which acts as a "thermodynamic sink" to afford the unexpected bromohydrin **119.1** (Scheme 121).



Scheme 121. Proposed route to unexpected bromohydrin **119.1**

7.44 Dihydroxylation

Reactions of osmium tetroxide with alkenes to give *syn*-vicinal diols was discovered in the early 1900's and was first published by Makowka in 1908.[274] Since then, this methodology has undergone incredible development with the introduction of a number of catalytic methods aimed at minimising the amount expensive and toxic osmium employed.[275] One of the most well-known and successful examples of employing catalytic amount of OsO_4 is the Upjohn process, which regenerates the active osmium species through the use of stoichiometric amounts of *N*-methylmorpholine *N*-oxide (NMO) as a sacrificial oxidant.[276] In the 1980's Sharpless developed an asymmetric dihydroxylation protocol on the basis of this earlier work, based on observations by Criegee that tertiary amines (e.g. pyridine) accelerated the reaction of osmium tetroxide with alkenes.[277-282] Continued development of their asymmetric methodology eventually led to a commercially available mixture of chiral ligand, oxidant and an osmium source being made available. These reagents are collectively known as AD-mix α and Ad-mix β, with opposite enantiomers of the $(DHQ)_2PHAL$ ligand potentially allowing for synthesis of the diol enantiomer of choice (Figure 35).

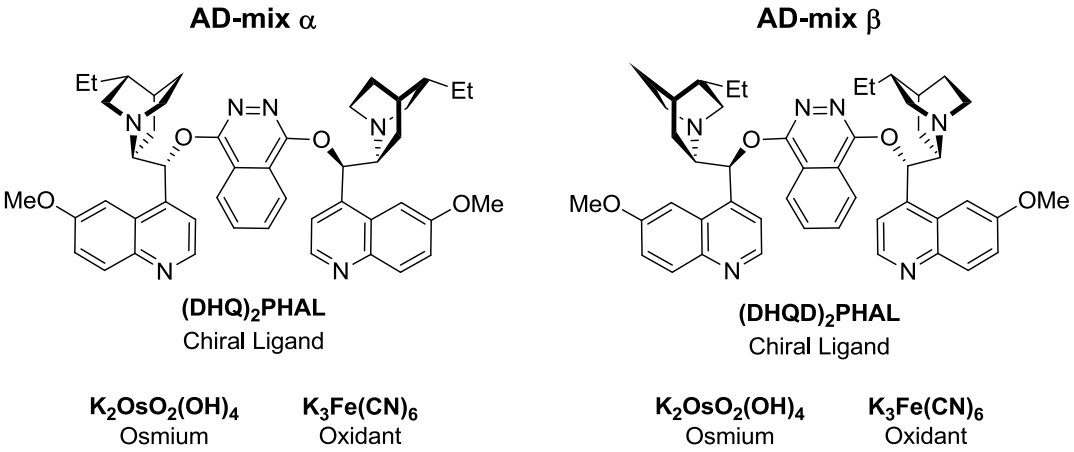
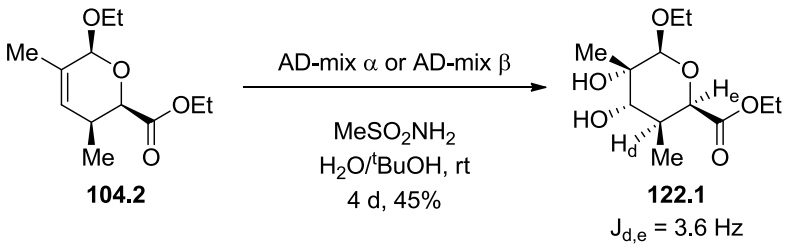


Figure 35. AD-mix α and AD-mix β

It was proposed that the use of AD-mix α or Ad-mix β for dihydroxylation of dihydropyran **104.2** could potentially afford both diastereomers of *syn*-diol **122.1** under catalyst control. However, it was found that irrespective of which Ad-mix was used, the same diol diastereomer **122.1** was obtained, indicating that substrate control overrides the ligand directing effect of the AD-mix reagents (Scheme 122). As seems to be common for use of AD-mix, the dihydroxylation reaction was slow, taking 4 days to afford diol **122.1** in only 45% isolated yield.



Scheme 122. Synthesis of diol **122.1**

The relative stereochemistry of diol **122.1** was assigned by NOESY NMR, with Hc demonstrating interactions with Hd due to the fact that they are both equatorial, whilst displaying no nOe interactions with Ha or He (Figure 36).

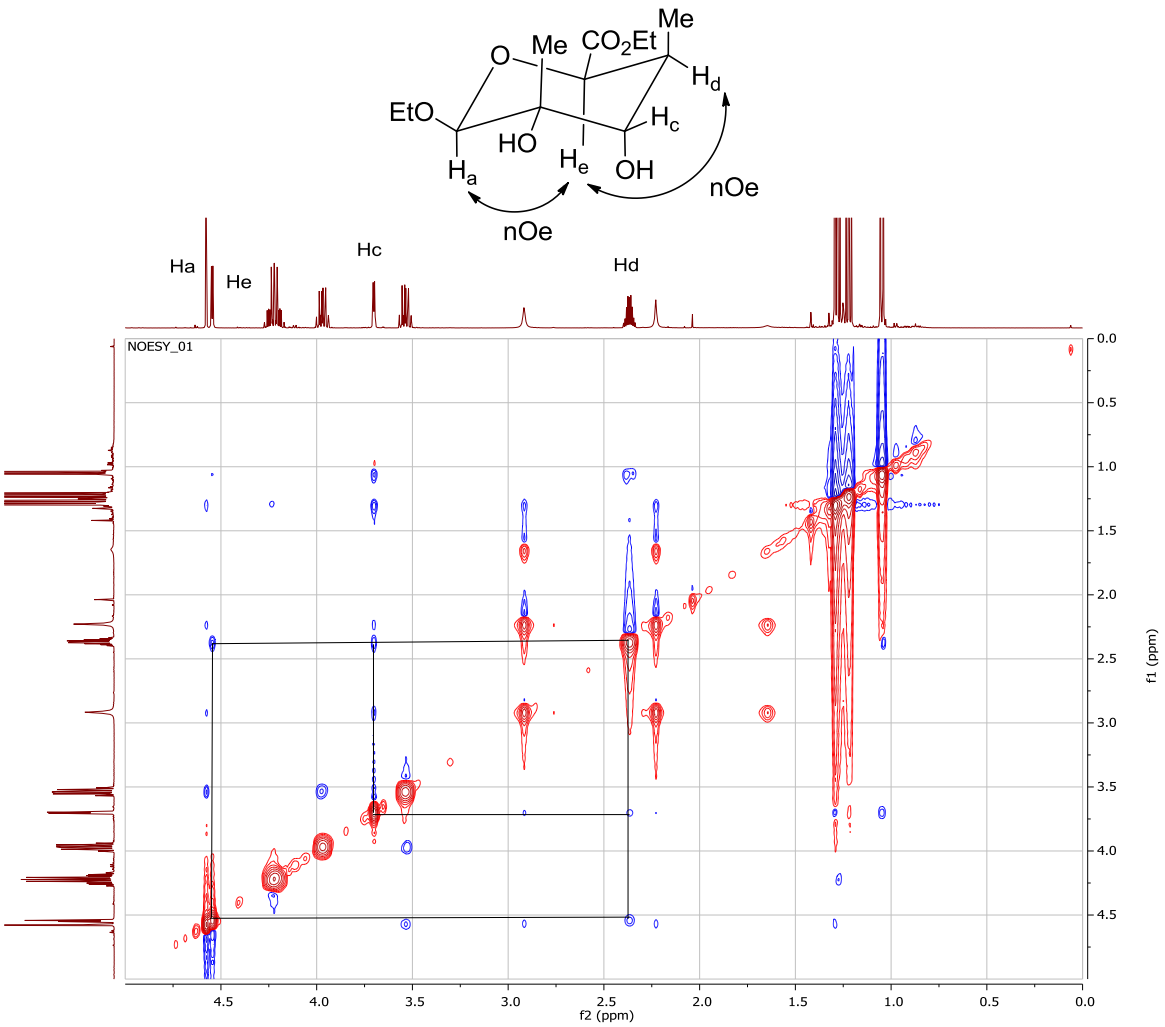
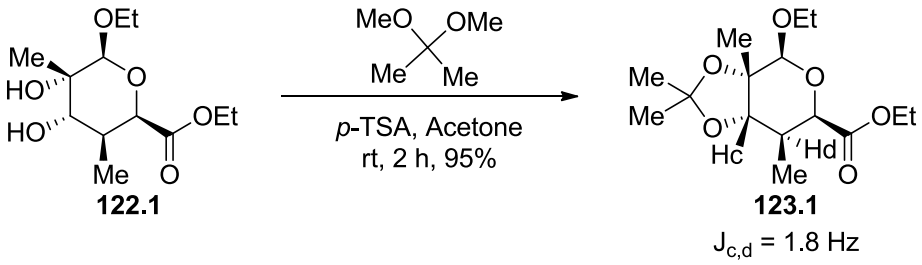


Figure 36. NOESY of diol **122.1**

In order to provide further confirmation of the configuration of the diol produced, it was decided to synthesise the more structurally rigid acetonide **123.1**, which was formed *via* treatment with dimethylacetal and pTSA in acetone in 95% yield (Scheme 123).



Scheme 123. Synthesis of acetonidel **123.1**

nOe analysis confirmed the relative stereochemistry as previously assigned with H_c having nOe interactions with H_d due to thier equatorial relationship, and no other interactions with any other protons of the pyran ring (Figure 37). The low coupling constant of 1.8 Hz for H_c and H_d also denotes an *anti*-relationship, with this low coupling constant value characteristic of an equatorial-equatorial relationship.

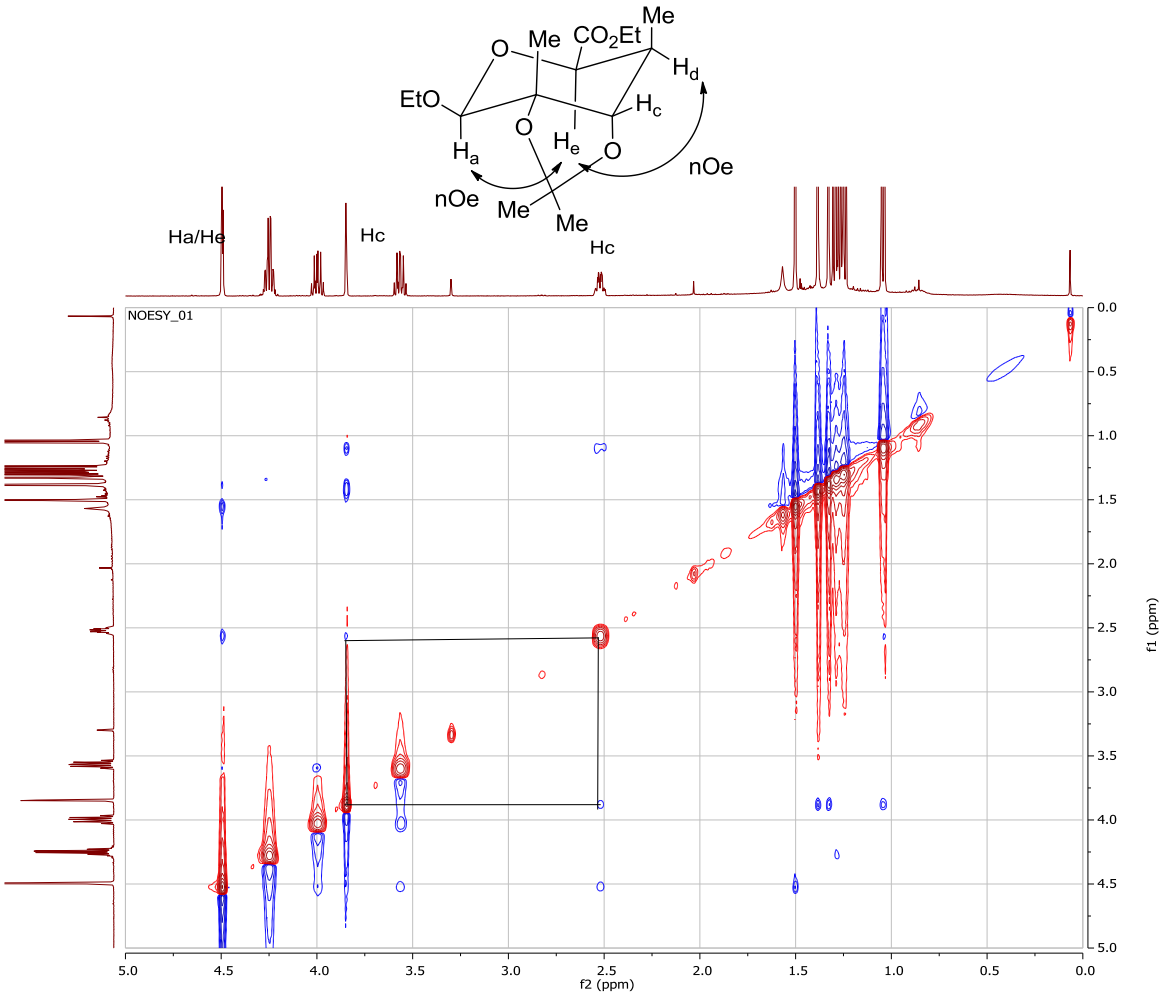


Figure 37. NOESY NMR of acetonide **123.1**

Dihydroxylation of dihydropyran **104.2** to give diol **123.1** gives rise to a stereotetrad containing a quaternary carbon centre, which is present as a stereotetrad fragment in the natural product yokonolide B, which is a novel inhibitor of auxin signalling (Figure 38).[283]

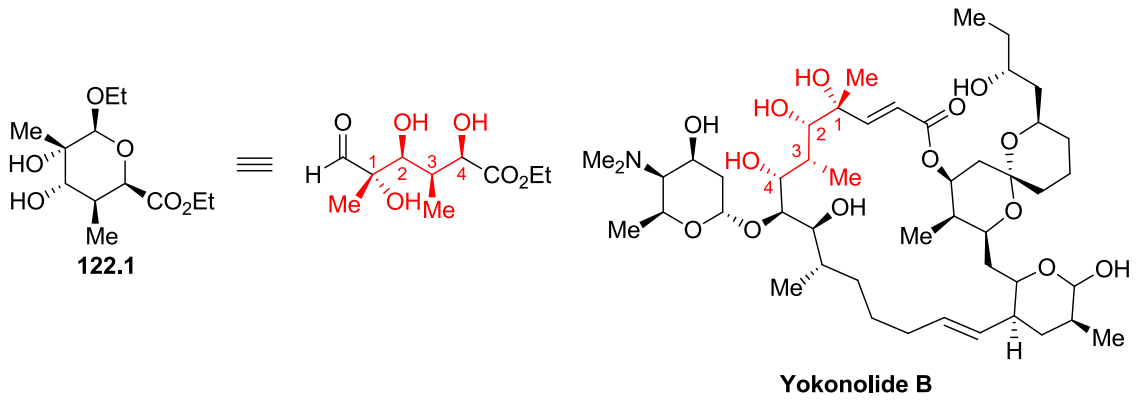
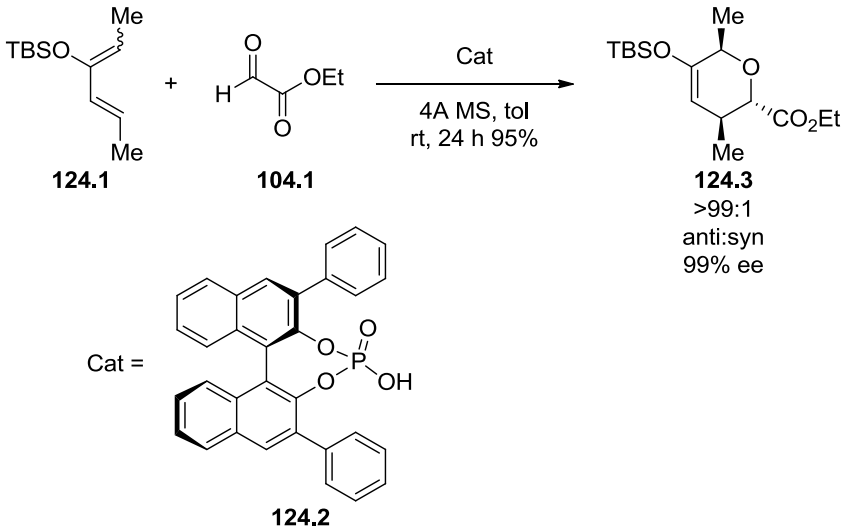


Figure 38. Yokonolide B

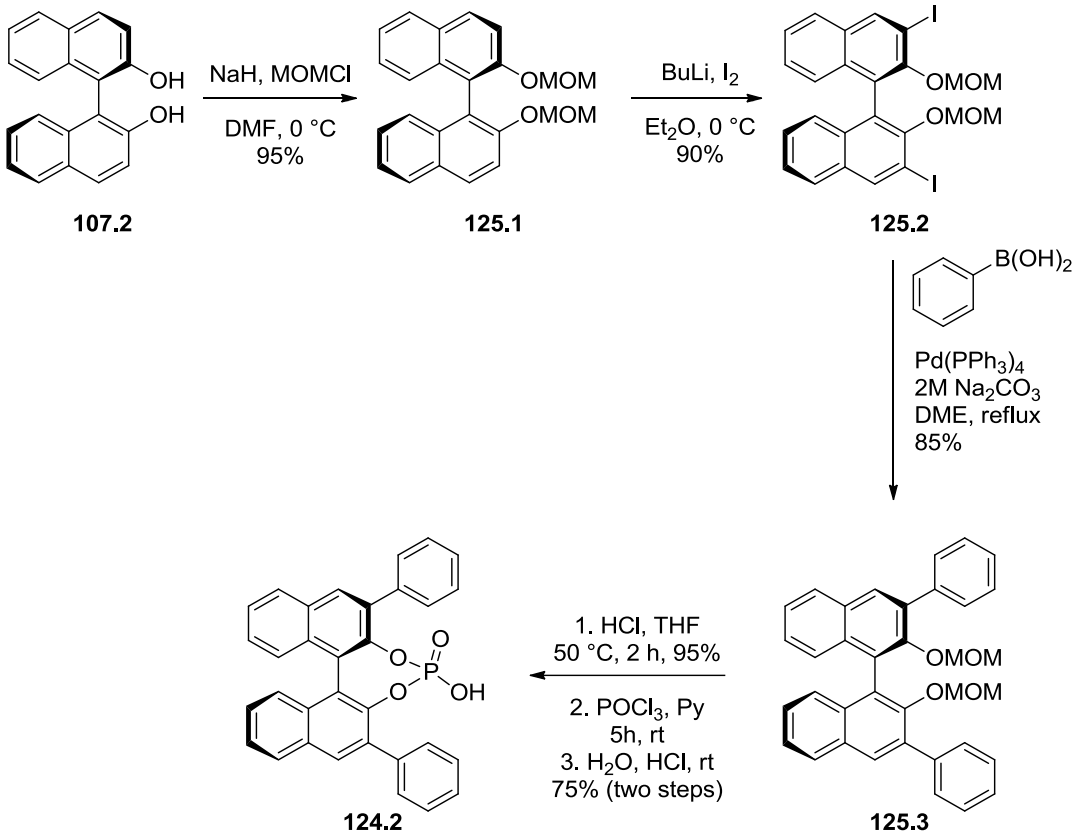
7.45 Epimerization

The aim of this project was to not only gain access to a library of chiral building blocks for polyketide synthesis, but also enable access to other possible diastereomeric tetrad combinations. An obvious simple change, which would double the current number of diastereomers accessible, would be to synthesise the *anti*-hetero Diels-Alder product, as opposed to the *syn*-hetero Diels-Alder product **104.2**. A publication by Terada in 2009 reported that use of chiral phosphoric acid **124.2**, as a chiral catalyst had afforded an *anti*-diastereoselective and enantioselective hetero-Diels-Alder reaction to be carried out.[284] In this instance, silyloxy diene **124.1** was coupled with ethyl glyoxalate **104.1** to give dihydropyran **124.3** in 95% yield with >99:1 *anti:syn* selectivity and 99% ee (Scheme 124).



Scheme 124. A chiral phosphoric acid catalysed *anti*-selective HDA reaction[284]

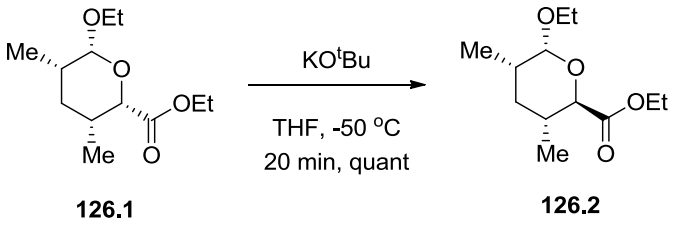
It was decided to synthesise chiral phosphoric acid **124.2** and apply this methodology to our system, with the synthesis of chiral phosphoric acid **124.2** beingperformed utilising the protocols of Kobayashi and Gestwicki as shown in Scheme 125.[285, 286]



Scheme 125. Synthesis of chiral phosphoric acid **124.2**

However, while Terada was able to demonstrate that this catalytic system was active for 1-alkoxy dienes for the formation of *anti*-HDA products, in our hands its HDA reactions proceeded to give the same *syn*-diastereomer **104.2** obtained previously observed using the Ti-BINOL catalyst **106.3**.

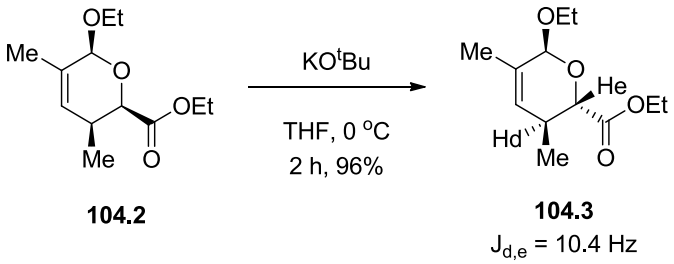
Therefore, it was decided instead to tackle this problem using a different approach. A literature search revealed that an epimerization protocol could potentially be a solution to this problem, since the Evans group had previously reported selective epimerization of pyran **126.1** (enantiomer of pyran **112.2**) through the use of potassium *tert*-butoxide as base at -50 °C in THF to give its epimer **126.2** in quantitative yield (Scheme 126).[264]



126.1 **126.2**

Scheme 126. Evans' selective epimerisation protocol[264]

This epimerisation protocol was applied to dihydropyran **104.2**, which on treatment with potassium *tert*-butoxide at 0 °C in THF for 2 h gave epimer **104.3** in 96% yield (Scheme 127).



104.2 **104.3**

Scheme 127. Epimerization of dihydropyran **104.2**

nOe analysis of dihydropyran **104.3** confirmed that epimerization had occured (when compared to the nOe of dihydropyran **104.2**), with the key proton-proton interactions that would indicate a *syn*-geometric relationship having disappeared (Figure 39). The analytical data for **104.3** also matches that for the minor diastereomer originally synthesised previously (see Scheme 104).

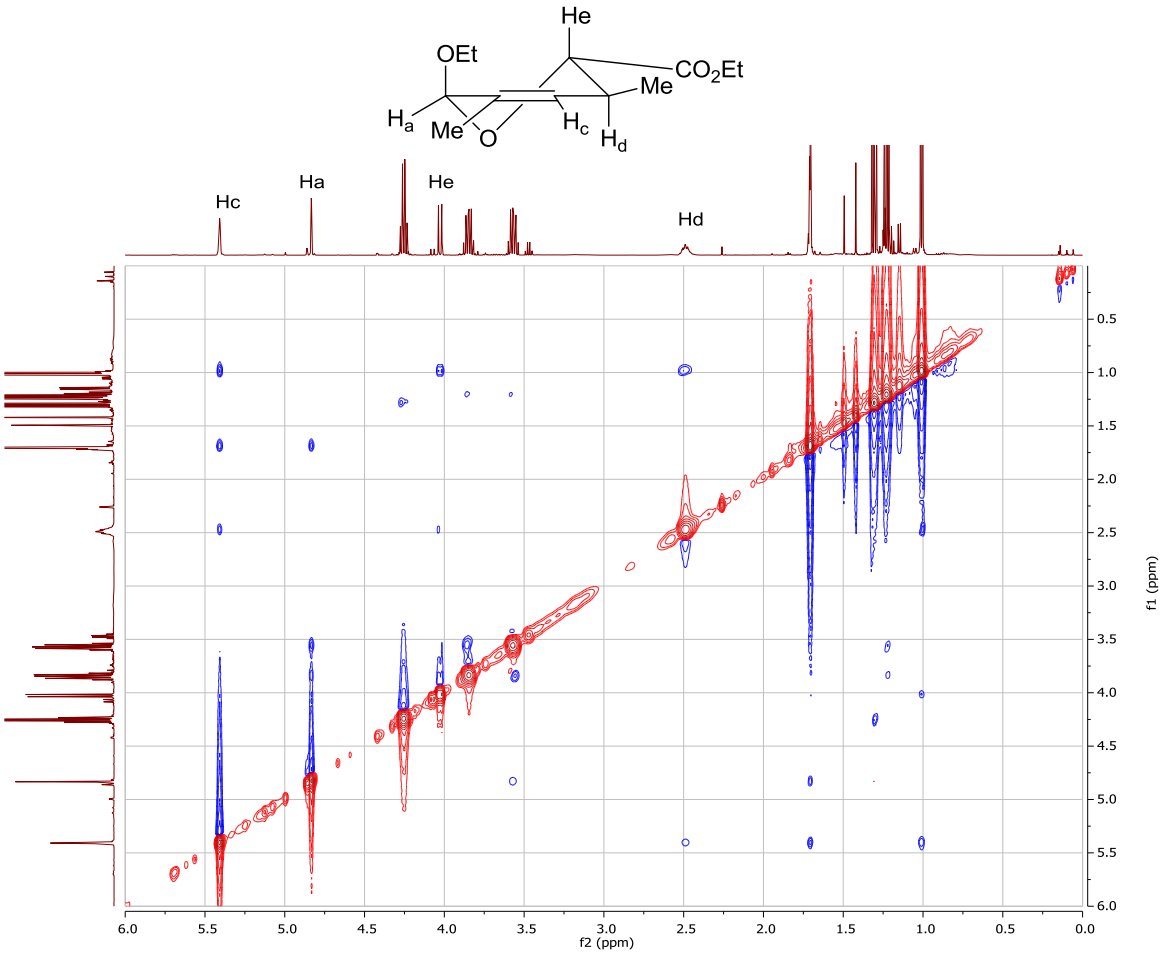
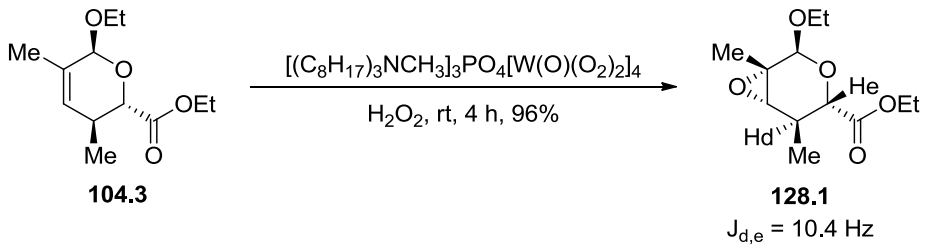


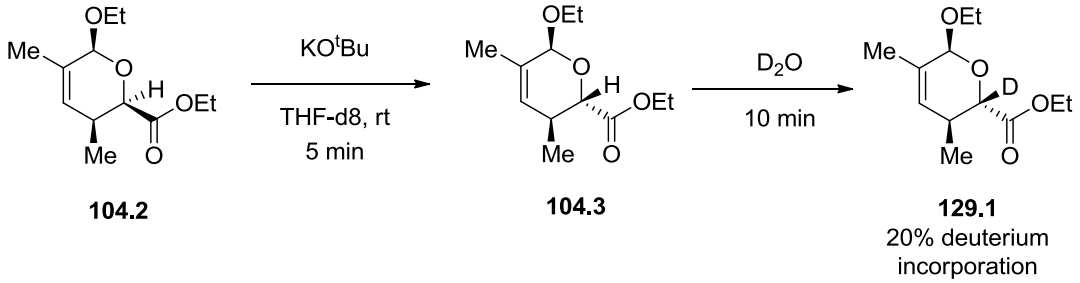
Figure 39. NOESY NMR of dihydropyran **104.3**

To demonstrate that the epimerization of this stereocentre does not affect the stereoselectivity of subsequent reactions, dihydropyran **104.3** was epoxidised to give epoxide **128.1** in 96% yield as the sole diastereomer. This result shows that the previous diastereoslective hydroboration/hydrodenation/dihydroxylation methods developed for dihydropyran **104.2** should also be applicable to dihydropyran **104.3** (Scheme 128).



Scheme 128. Epoxidation of dihydropyran **104.1**

To further understand this epimerization reaction a deuterium experiment was performed. The reaction was conducted in deuterated THF with KO^{t}Bu at room temperature, after 5 min a small amount of D_2O was then added to the NMR tube, with ^{1}H NMR spectroscopic analysis showing a 20% deuterium incorporation (Scheme 129). This results suggests that the epimerization proceeds through deprotonation at the ester proton, it also suggests that the deprotonation event of the epimerized dihydropyran **104.3** occurs at a much slower rate than for dihydropyran **104.2**, as shown by the low deuterium incorporation.



104.2 **104.3** **129.1**
20% deuterium incorporation

Scheme 129. Deuterium incorporation experiment for dihydropyran **104.2**

7.451 Computational Studies on Epimerization of Dihydropyran 104.2

In an attempt to fully understand how this epimerization process is able to achieve complete stereocentre inversion, density functional theory (DFT) computational studies on the two diastereomers **104.2** and **104.3** were undertaken.

All calculations were performed using the Gaussian09 suite of codes (revision D.01).[287] Geometries were fully optimised without any symmetry or geometry constraints. The calculations were all carried out using a temperature of 298 K and solvent effects in tetrahydrofuran considered using conductor-like polarisable continuum model (CPCM). The nature of all the stationary points as minima were verified by calculations of the vibrational frequency spectrum. Free energies were calculated within the harmonic approximation for vibrational frequencies.

Figure 40 shows a summary of the data gained from these computational analysis, with the Gibbs free energy of pyran **104.3** set to zero so that a comparison to the other three conformers can be made. As can be seen both the low energy *syn*-conformers of dihydropyran **104.2** possess Gibbs free energies significantly higher than the epimerized product **104.3** (Figure 41).

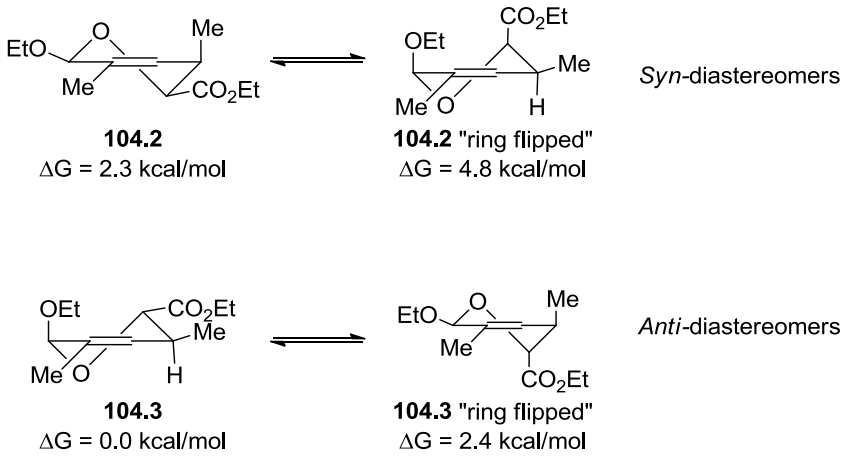


Figure 40. Computed Gibbs free energies at the 6-311++G(d, p)/B3LYP/cpcm=THF/298 K level of theory for the epimerization of dihydropyran **104.2**

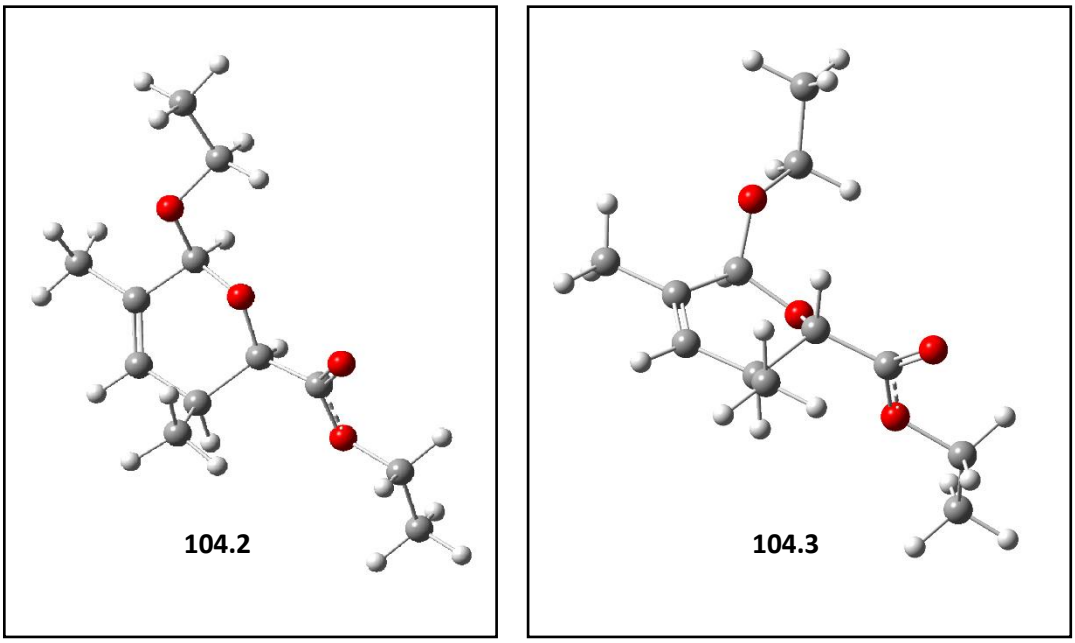


Figure 41. Lowest energy conformers of dihydropyran **104.2** and **104.3**

7.5 Dihydropyran Analogue Synthesis

While the stereotetrad is present in a wide range of polyketide natural products, access to other motifs such as deoxy-1,3-methyl-methyl substitution would also be useful to access other types of polyketide natural product targets (Figure 42). Furthermore, access to this type of methodology would potentially allow for structure activity relationships (SAR) study to be performed to help decipher which structural elements in a natural product were responsible for their biological activity, by allowing facile access to non-natural analogues.

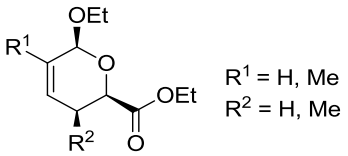
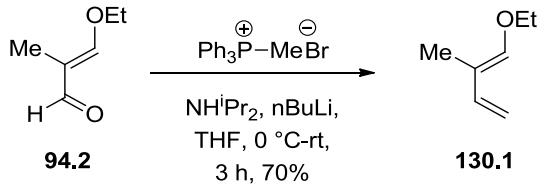


Figure 42. Dihydropyran analogues

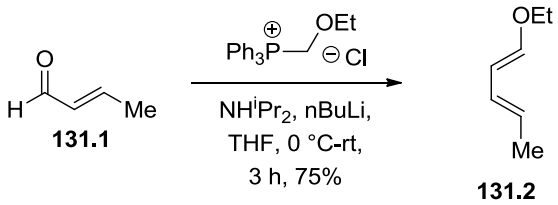
7.51 Synthesis of Diene Analogues

In order to access these dihydropyran analogues the diene utilized in the hetero-Diels-Alder methodology had to be altered. Diene **130.1** was first targeted as it could be accessed from aldehyde **94.2** which was an intermediate that had been generated previously on route to diene **96.1**. Employing methyltriphenylphonsphonium bromide in the Wittig reaction of **94.2** enabled the desired diene **130.1** to be prepared in 70% yield (Scheme 130).



Scheme 130. Synthesis of diene **130.1**

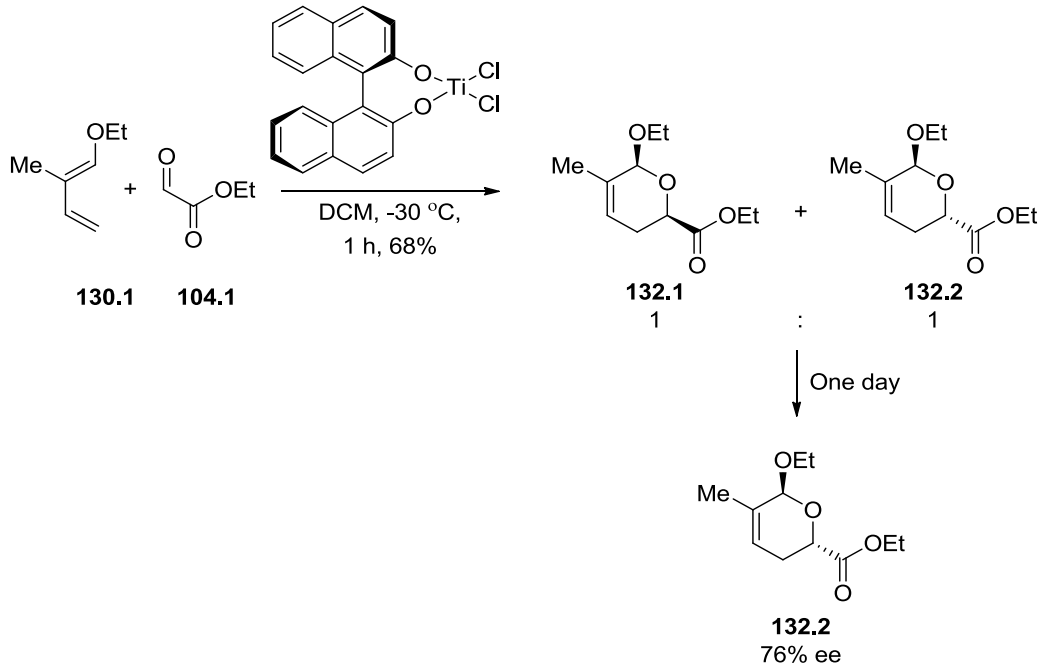
Wittig chemistry was also utilized for the synthesis of diene **131.2**, with crotonaldehyde **131.1** being reacted with (ethoxymethyl)triphenylphosphonium chloride under standard Wittig conditions to afford (*E. E*)-diene **131.2** in 75% yield (Scheme 131)



Scheme 131. Synthesis of (E. E)-diene **131.2**

7.52 Dihydropyran Analogues Synthesis

Dienes **130.1** and **131.2** were then subjected to the catalytic enantioselective hetero-Diels-Alder conditions previously utilized for the synthesis of dihydropyran **104.2** in 99% ee. The HDA reaction of diene **130.1** proceeded in 68% yield with poor diastereoselectivity to afford an epimeric mixture of **132.1** and **132.2** in a ratio of 1:1. However, it was found that over time, this mixture readily epimerized to give a single diastereomer assigned as dihydropyran **132.2** in 68% yield and 76% ee (Scheme 132).



Scheme 132. Synthesis of dihydropyran **132.2**

The configuration of dihydropyran formed after epimerization was assigned as the *anti*-diastereomer **132.2**, from consideration of its nOe NMR spectrum. As shown in Figure 43, the key nOe interactions between Ha and He which would denote a *syn* relationship as if present in the nOe of dihydropyran **104.2** were not present, suggesting that the *anti*-diastereomer is the final product of this HDA/epimerisation protocol.

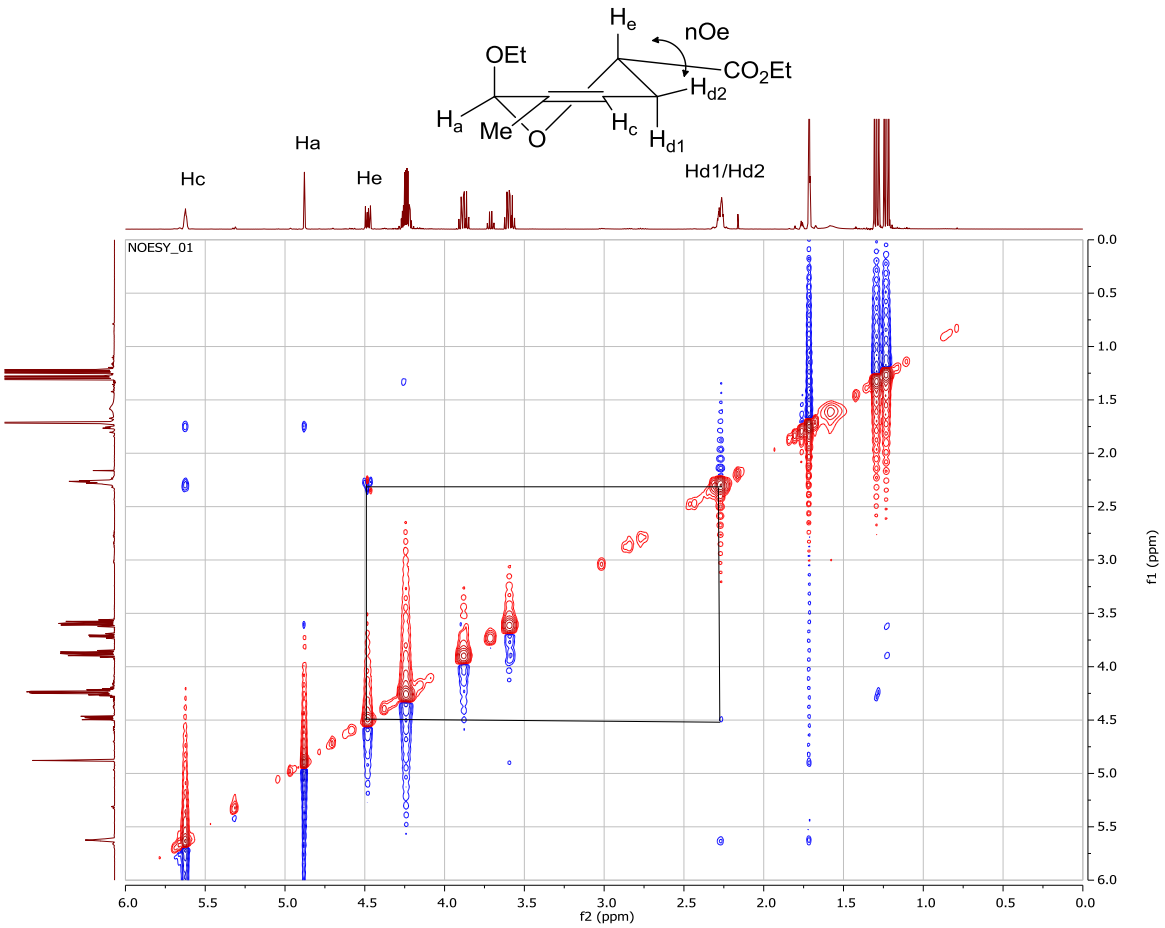
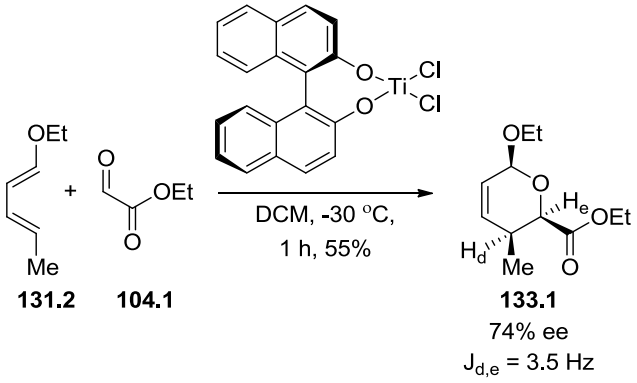


Figure 43. NOESY NMR of dihydropyran **132.2**

The HDA reaction of diene **131.2** proceeded with good diastereoselectivity to give a single diastereomer of dihydropyran **133.1** in 55% yield and 74% ee (Scheme 133).



131.2 **104.1**

133.1
74% ee
$J_{d,e}$ = 3.5 Hz

Scheme 133. Synthesis of dihydropyran **133.1**

Once again the relative stereochemistry of this diastereomer was confirmed by nOe NMR with the key interactions between Ha, Hc and He confirming the *syn* geometry, and with the $J_{d,e}$ coupling constant of 3.5 Hz being indicative of a *syn*-relationship.

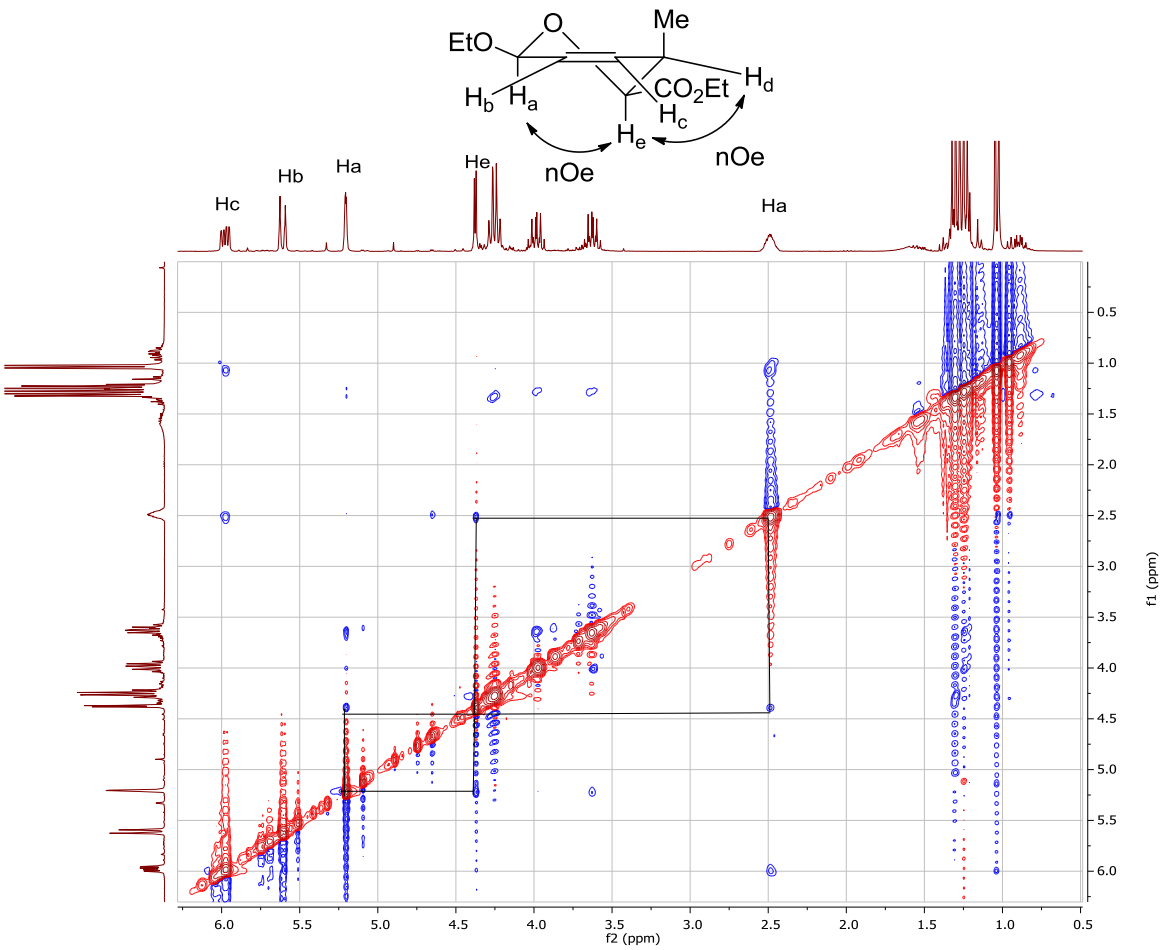


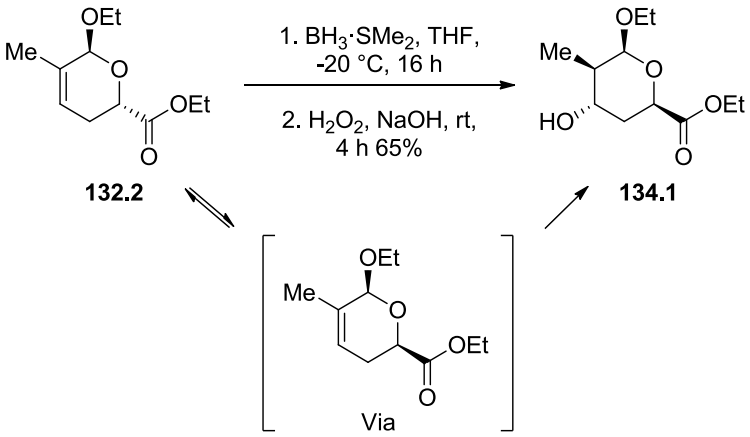
Figure 44. NOESY NMR of dihydropyran **133.1**

The ee's of both dihydropyran **132.2** and **133.1** of 76% and 74% ee were relatively low when compared to the parent dihydropyran **104.2**, which was formed in 99% ee. It is believed that with further optimization the ee of both these reactions should be able to be increased to a level much closer to that of dihydropyran **104.2**, however, due to time constraints this optimisation study will be conducted in the near future.

7.53 Dihydropyran Analogues Derivatisation

As with the original chiral dihydropyran template **104.2**, it was hoped that all subsequent derivatization reactions performed on analogues **132.2** and **133.1** would proceed

stereoselectively to afford a single diastereomer. Hydroboration of dihydropyran **132.2** proceeded well to afford a single diastereomer in 65% yield (Scheme 134). Surprisingly upon further characterisation is appeared that the *syn*-diastereomer had been formed. This would suggest that hydroboration had occurred in conjunction with an epimerisation event. This could potentially occur in solution either before borane addition, or after the hydroboration step had occurred. It is believed to be the first option, where epimerisation of dihydropyran **132.2** occurs before borane addition. This is due to evidence of unreacted dihydropyran **132.1** being present in the crude ^{1}H NMR (Scheme 134).



Scheme 134. Hydroboration of dihydropyran **132.2**

Examination of the nOe NMR confirms the *syn* relative stereochemistry, with key interactions between Ha and Hf showing that these two protons are present on the same face of pyran ring, confirming their *syn*-relationship. Importantly, as well Hc shows no interactions with Ha, Hb and crucially Hf, confirming its *anti*-relationship to other protons (Figure 45).

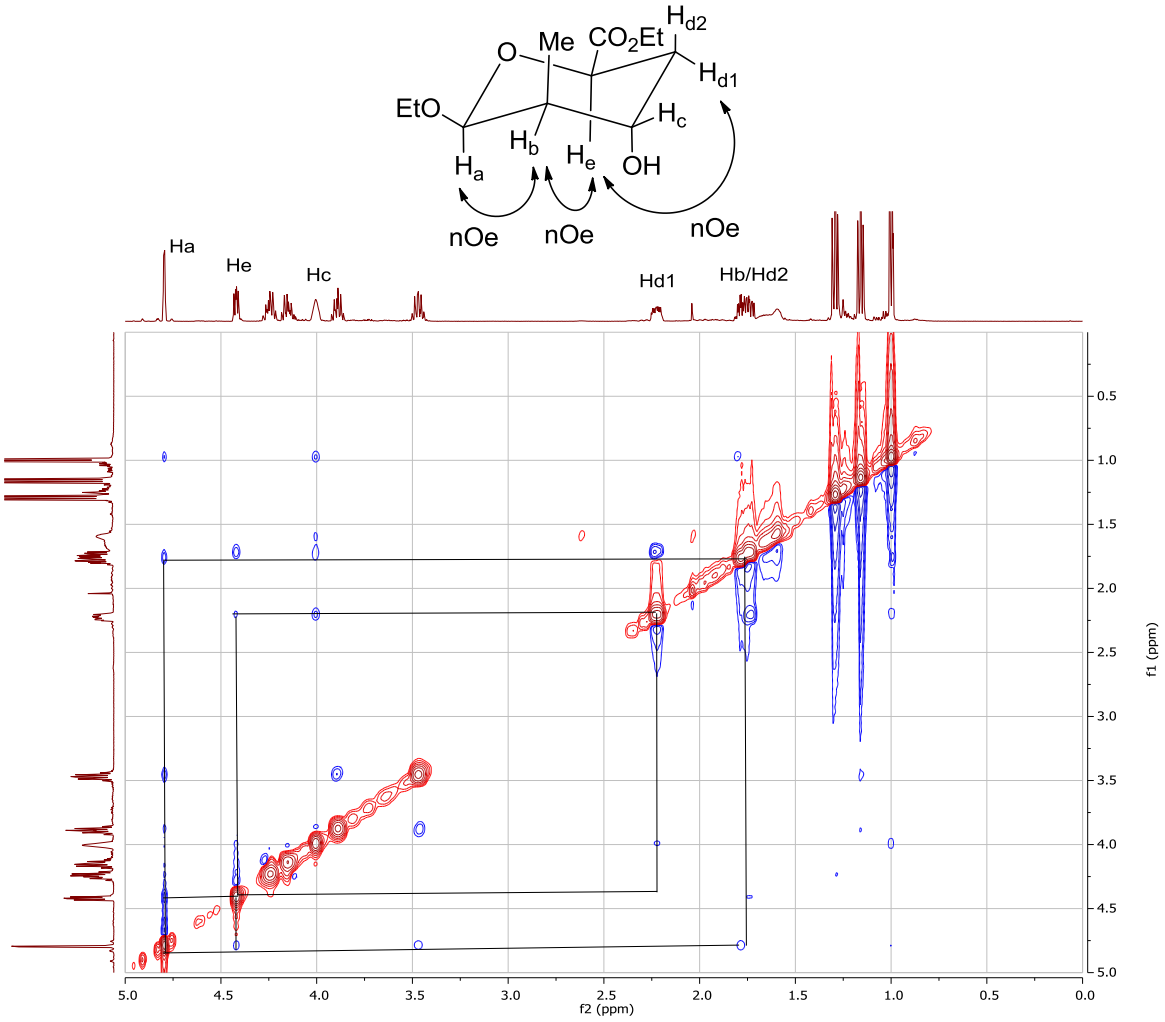


Figure 45. NOESY of pyran **134.1**

Pyran **134.1** contains a sterotriad with *syn-syn* relative stereochemistry, which contains the same relative stereochemistry as that present in the recently discovered marine polyhydroxy polyketides nahuoic acid D and nahuoic acid E (Figure 46).[288]

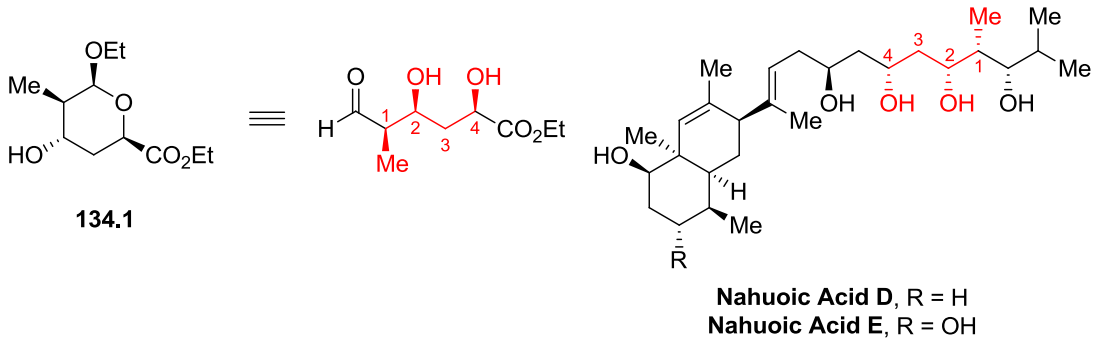
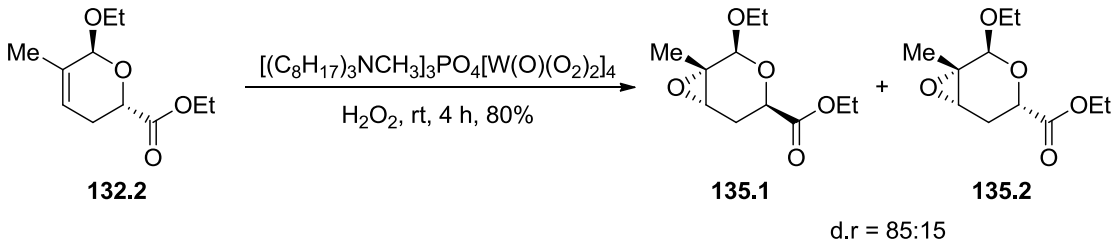


Figure 46. Nahuoic acid D and nahuoic acid E[288]

Epoxidation of dihydropyran **132.2**, using the Venturello conditions used previously, resulted in a mixture of *syn*-epoxide **135.1** and *anti*-epoxide **135.2**. The two epoxides were produced in 80% yield and a diastereomeric ratio of 85:15 in favour of the *syn*-epoxide **135.1** (Scheme 135).



Scheme 135. Epoxidation of dihydropyran **132.2**

Examination of the nOe NMR confirmed the all *syn* relative stereochemistry of the major diastereomer, with key interactions between Ha and He showing that these two protons are present on the same face of the pyran ring, thus confirming their *syn*-relationship (Figure 47).

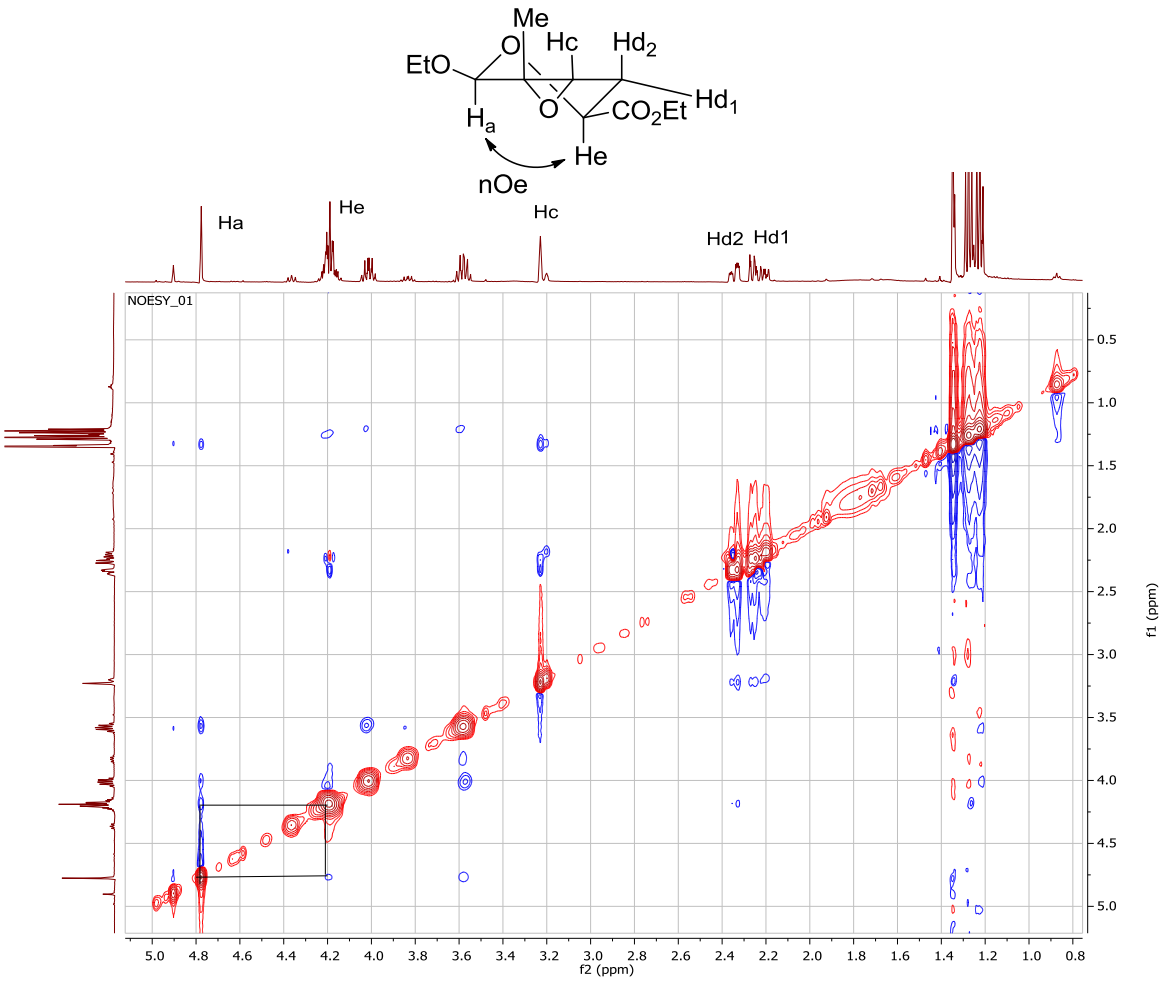
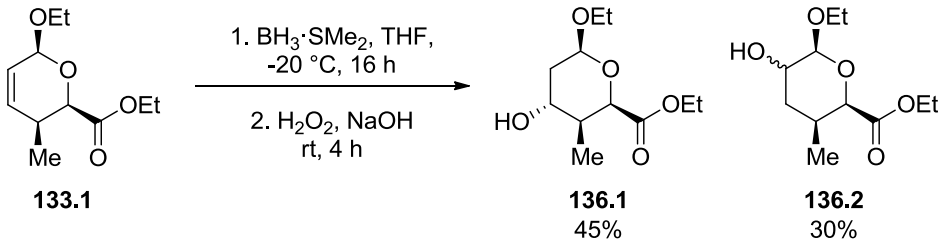


Figure 47. NOESY of epoxide **135.2**

Hydroboration of dihydropyran **133.1** led to the formation of two regioisomers pyran **136.1** and pyran **136.2** in a 3:2 ratio in an overall yield of 75% (Scheme 136). This loss of regiocontrol is due to the absence of the alkene methyl groups that were present in dihydropyrans **104.2** and **132.2**. Pyran **136.1** was formed as a single diastereomer, showing that the directive nature of the cyclic system is still effective. However, the minor pyran **136.2** was formed as a 1:1 mixture of diastereomers (unassigned), as evidenced by doubling of the peaks present in both the ^{1}H and ^{13}C NMR spectra.



Scheme 136. Hydroboration of pyran **133.1**

COSY NMR was used to help identify the structure of pyran **136.1**, which revealed that Hb_1 and Hb_2 showed coupling to each other and with Hc (the hydroxyl proton) (Figure 48).

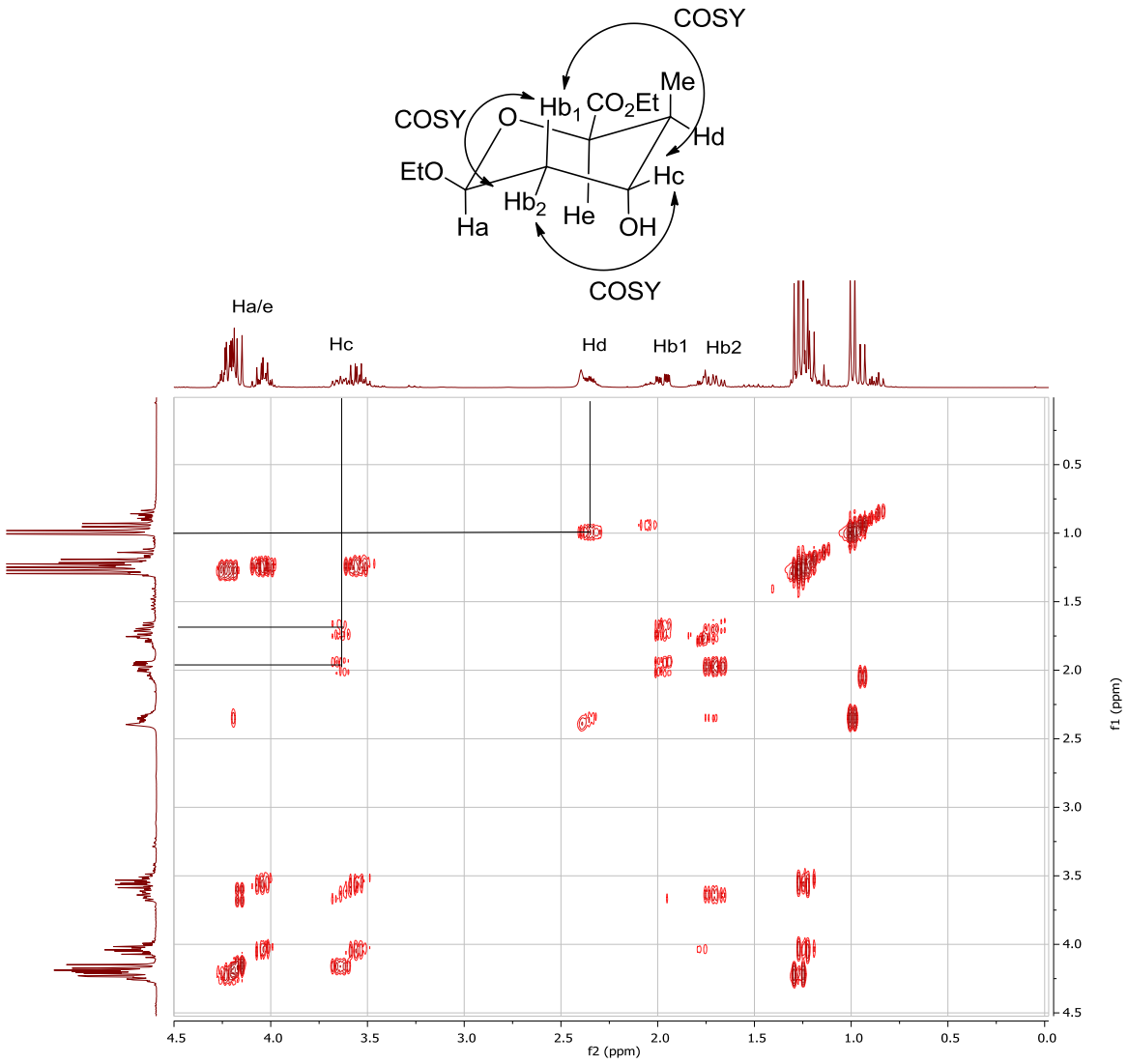


Figure 48. COSY NMR of pyran **136.1**

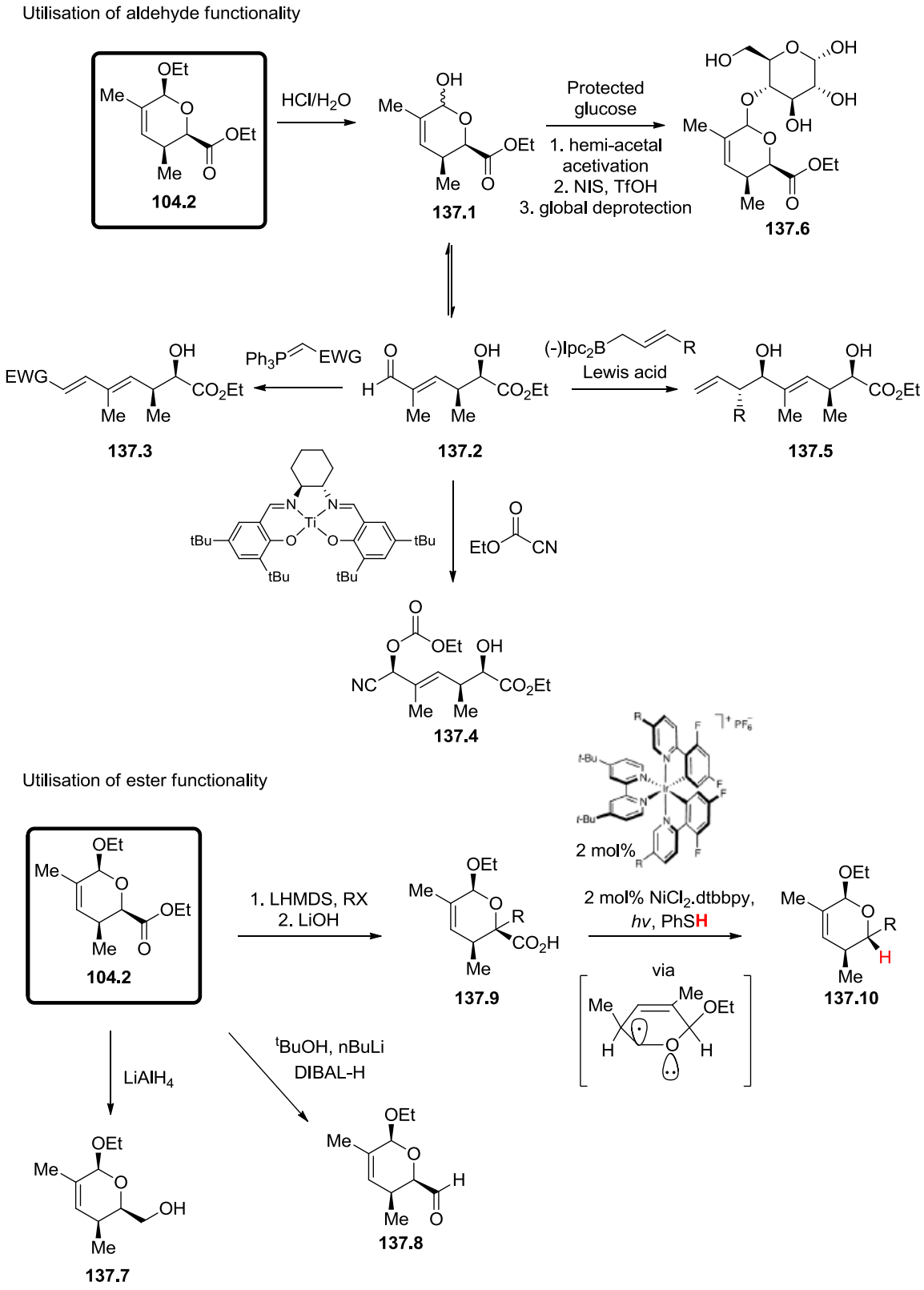
7.6 Further Dihydropyran Derivatization

By gaining access to enantiomerically enriched dihydropyrans **104.2**, **132.2** and **133.1** as the well as their subsequent derivatives, methodology has been developed to allow for rapid derivatisation of chiral templates with potential for the synthesis of polyketides. These dihydropyran compounds possess bi-functional aldehyde and ester groups at their termini, which can potentially be functionalised in a selective manner. This would potentially allow access to the "plug and play" approach originally devised at the outset of this project, with a representative range of transformations that could be utilised to achieve this aim presented in Scheme 137.

Hydrolytic cleavage of the masked acetal of dihydropyran **104.2** would give access to a "sugar" analogue **137.1**, that would exist in both its cyclic hemi-acetal form **137.1** and also as its acyclic aldehyde **137.2**. This aldehyde represents a highly reactive functional handle that can be derivatized in a number of ways, such as through the use of Wittig olefination chemistry to give diene **137.3**. Another method of utilising this aldehyde functionality would be through titanium salen catalysed asymmetric synthesis of cyanohydrin ethyl carbonates,[289] which would potentially give access to β-aminoalcohols and γ-azido-α,β-unsaturated nitriles. This aldehyde functionality could also be utilised to carry out boron or silicon allylation chemistry to allow access homoallylic alcohol **137.5**, which are a highly prized class of synthetic intermediates for the construction of a wide variety of complex polyketides.[290] Sugar compound **137.1** can also be utilised as a synthetic reagent in its own right, utilising carbohydrate chemistry to form glycosidic bonds to natural sugars, to give rise to potentially exciting polyketide-sugar hybrids **137.6**.

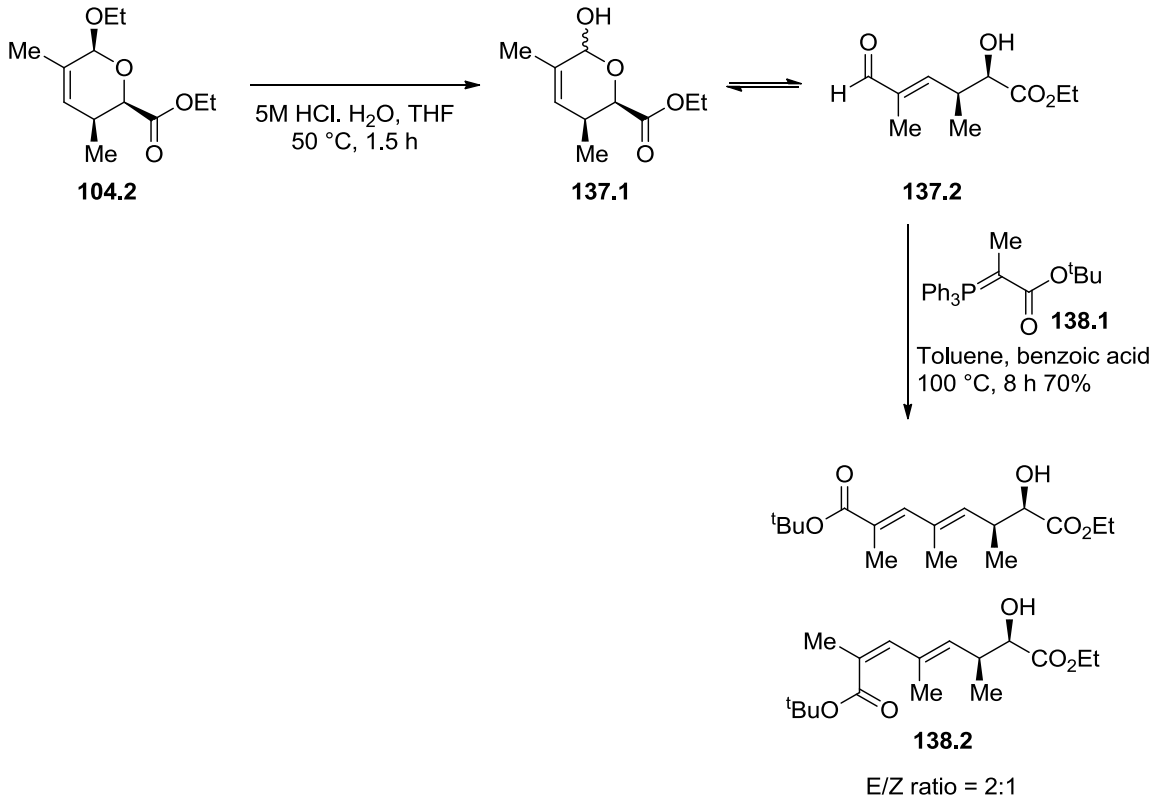
The ester functional handle present in dihydropyran **104.2** can also be utilised in a number of ways. Global reduction would give rise to primary alcohol **137.7**, with activation as its mesylate/tosylate (or as a halogen *via* Appel reaction), enabling a wide range of nucleophiles to be introduced into the compound. However, use of a mild selective reducing agent such as lithium diisobutyl-*tert*-butoxyaluminium hydride (LDBBA) which is formed through a combination of ^{t}BuOH, nBuLi and DIBAL-H, might allow access to aldehyde **137.8**, which could then be subjected to the wide range of derivatization chemistries available for aldehyde **137.2**. A further more complex elaboration of dihydropyran **104.2** would be to utilise the chemistry developed for epimerization of pyran **104.2**. Therefore, deprotonation of pyran **104.2** at its C_6-position would afford an enolate, which could be alkylated with a range of electrophiles. Hydrolysis of the ester functionality to afford carboxylic acid **137.9**, would then allow for implementation of photoredox decarboxylation chemistry. Decarboxylation of carboxylic acid

137.9 through irradiation of an Ir/Ni catalytic system, would potentially afford advanced pyran intermediates **137.10** containing different side-chains with high levels of diastereocontrol. The stereoselectivity of this process would be controlled by the formation of an antiperiplanar radical intermediate preferentially adopting a *trans*-diaxial orientation due to the anomeric effect. While the example shown replaces the carboxylic acid with a proton, this could also be used as an opportunity to introduce a wide range of new functionality. For example, recent reports by MacMillan and Waser have demonstrated how photoredox chemistry can be used to replace carboxylic acids groups with alkene and alkynyl groups,[291, 292] which would represent a highly efficient way of joining together fragments enroute to a complex natural product (Scheme 137).



Scheme 137. Potential synthetic elaborations of dihydropyran **104.2**

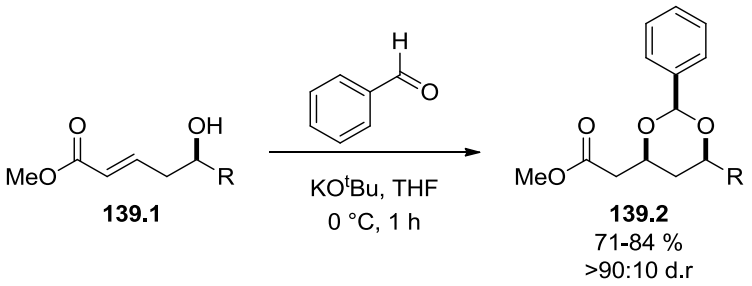
As proof of concept that these dihydropyrans could be further elaborated, it was decided to pick two of these examples shown for the further derivatization of dihydropyran **104.2**. It was decided to first investigate utilization of the masked aldehyde functionality, of **104.2** through a Wittig-olefination reaction. Treatment of dihydropyran **104.2** with mild acid at 50 °C led to formation of sugar-like intermediate, which exists in both its cyclic lactol **137.1** form and an acyclic aldehyde **137.2**. The aldehyde group was then intercepted by treatment with phosphonium ylide **138.1** to give diene **138.2** in a 70% yield over the two steps. Diene **138.2** was formed as an inseparable 2:1 ratio of *E:Z* geometric isomers, which contained orthogonally addressable ester groups that would allow for selective derivatisation (Scheme 138).



Scheme 138. Exploiting the masked aldehyde functionality of **104.2** for the synthesis of diene **138.4**

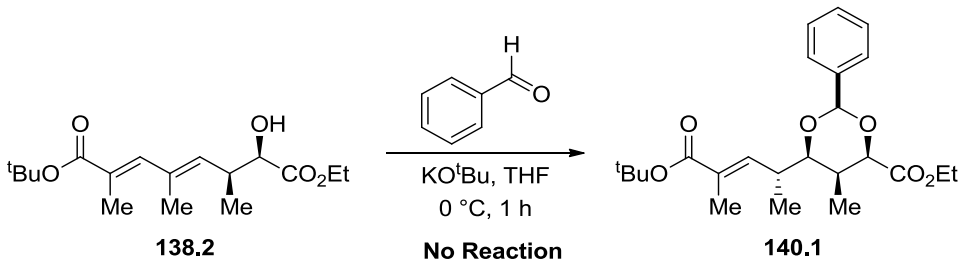
It was hoped that diene **138.2** would be set up, to allow for the utilization of Evans methodology for the diastereoselective synthesis of a protected syn 1,3-Diols.[293] The Evans methodology proceeds through formation of an acetal alkoxide which is then able to act as tethered oxygen nucleophile. This nucleophile is then able to undergo diastereoselective

intramolecular conjugate addition to a Michael acceptor in a stereoselective manner to afford a benzylidene acetal **139.2** (Scheme 139). This methodology represents a potentially exciting way of installing a hydroxyl group (through subsequent hydrolysis of the benzylidene acetal) in a stereoselective manner.



Scheme 139. Evans methodology for diastereoselective synthesis of protected syn 1,3-diols.[293]

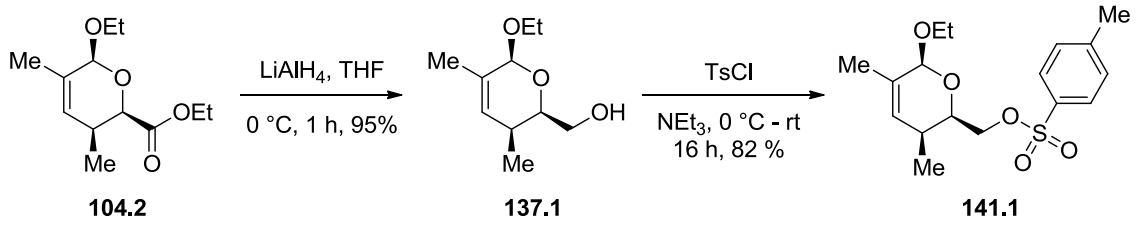
It was hoped that this Evans' methodology could be applied to vinylogous diene **138.2**, where it was proposed that this conjugated system would also be able to undergo a similar intramolecular conjugate addition. However, this reaction proved to be unsuccessful (Scheme 140), which is believed to be due to the fact that the distal alkene is not sufficiently conjugated, and may possess more "normal" electron rich alkene character. Evidence of this can be seen when similar diene systems are subjected to dihydroxylation conditions, with only the remote alkene group undergoing dihydroxylation.[294] It is hoped that with more investigation this methodology could be applied to diene **138.2**, however, due to time constraints this was beyond the current scope of this thesis.



Scheme 140. Unsuccessful attempt at employing Evans methodology for the diastereoselective synthesis of protected syn *1,3*-diols

Finally, as a method of showing the utility of the ester functionality it was decided to perform a global reduction, and then demonstrated that the resultant alcohol could be activated for further derivatisation. Reduction of ester **104.2** through treatment with $LiAlH_4$ afforded

alcohol **137.7** in 95% yield, leaving the hemi-acetal and alkene functionality untouched. This alcohol presents an excellent intermediate for further elaboration, *via* its corresponding tosylate **141.1**, which was prepared in 82% yield using standard (Scheme 141). Tosylate **141.1** is a key compound to demonstrate how these chiral building blocks could be implemented into a synthetic route, since it can be reacted with a range of nucleophiles to provide advanced intermediates for polyketide synthesis.

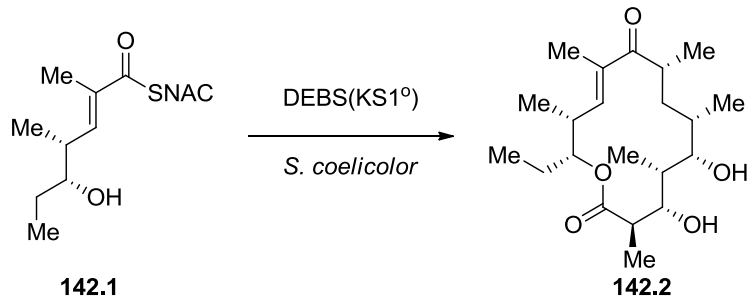


104.2 **137.1** **141.1**

Scheme 141. Route to exploiting the ester functionality

8.0 Future Work

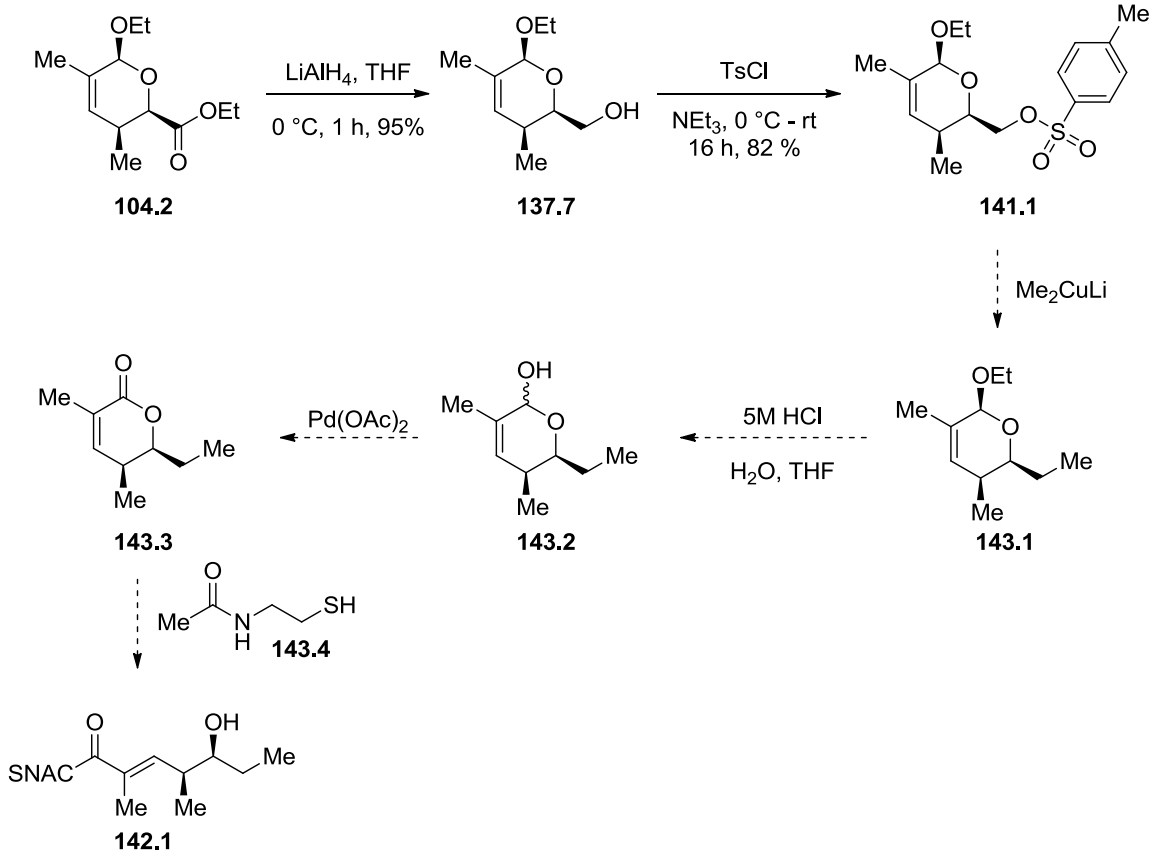
There are a number of ways in which this research project could be taken forward. An obvious choice would be to identify a late stage synthetic intermediate of a polyketide natural product and conduct a formal synthesis where the methodology developed leads to a significant reduction in step count and a more efficient synthesis. However, an equally important application where this methodology could have a large impact is in the field of precursor directed biosynthesis.[295-298] For example, the Khosla and Cane groups have conducted extensive research into precursor-directed biosynthesis of 16-membered macrolides by the erythromycin polyketide synthase. They were able to utilize a range of SNAC thioester precursors (such as alkene **142.1**) as substrates for deoxyerythronolide B synthase (DEBS) a polyketide synthase. The synthase was shown to be able to use these substrates to construct a series of macrolides. By varying the diastereomer and functionality of the substrate used, a range of natural and non-natural polyketides could be synthesised (Scheme 142).[295-298]



142.1 **142.2**

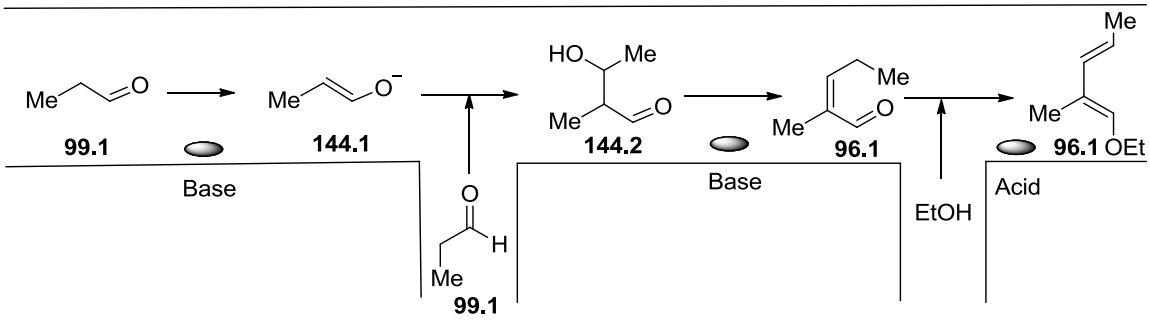
Scheme 142. Precursor-directed biosynthesis of macrolide **142.2**

By utilizing the methodology developed throughout this project, quick and efficient access to this type of substrate could be achieved, that would allow variation of the functionality and diastereoselectivity incorporated into the corresponding macrolide. Shown below is a proposed route for the synthesis of SNAC thioester precursor **142.1**. Substitution of the tosyl group of pyran **142.1** with a carbon nucleophile (e.g. Me_2CuLi) could then afford alkene **143.1.** Hemi-acetal formation, followed by oxidation would generate lactone **143.3**, which if treated with *N*-Acetylcysteamine **143.4** would generate thioester **142.1** as a precursor for feeding studies (Scheme 143).



Scheme 143. Proposed route to biosynthetic precursor **142.1**

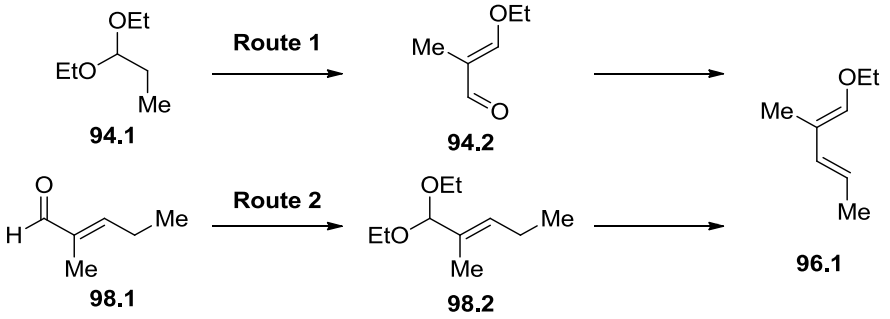
Further development of diene synthesis might also be considered, with a potential route to attempt to utilise flow technology shown in Scheme 144. For example, treatment of propionaldehyde **99.1** with a solid-supported base 'in-flow' should generate an enolate species **144.1** that will be flowed into the stream of another aldehyde (shown propionaldehyde **99.1**) to afford a homo-aldol product **144.2** that could then be dehydrated *via* contact with base to afford an enone **98.1**, that could be reacted with EtOH/H^+ to afford diene **96.1** (Scheme 144).



Scheme 144. Proposed "in flow" diene synthesis

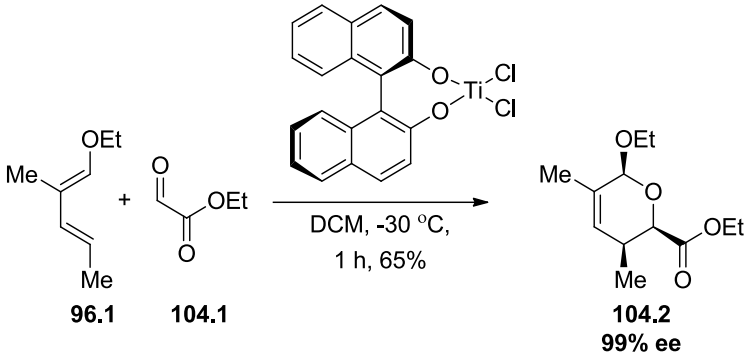
9.0 Conclusion

A potential route towards the synthesis of a library of building blocks for the synthesis of polyketide natural products has been presented. Two reliable synthetic routes to multigram quantities of substituted 1-alkoxy dienes have been established. The first of these approaches utilises a non-aromatic Vilsmeier reaction, followed by Wittig chemistry to construct the conjugated diene. The second more efficient route involves acetal formation, followed by base facilitated elimination resulting in diene formation.



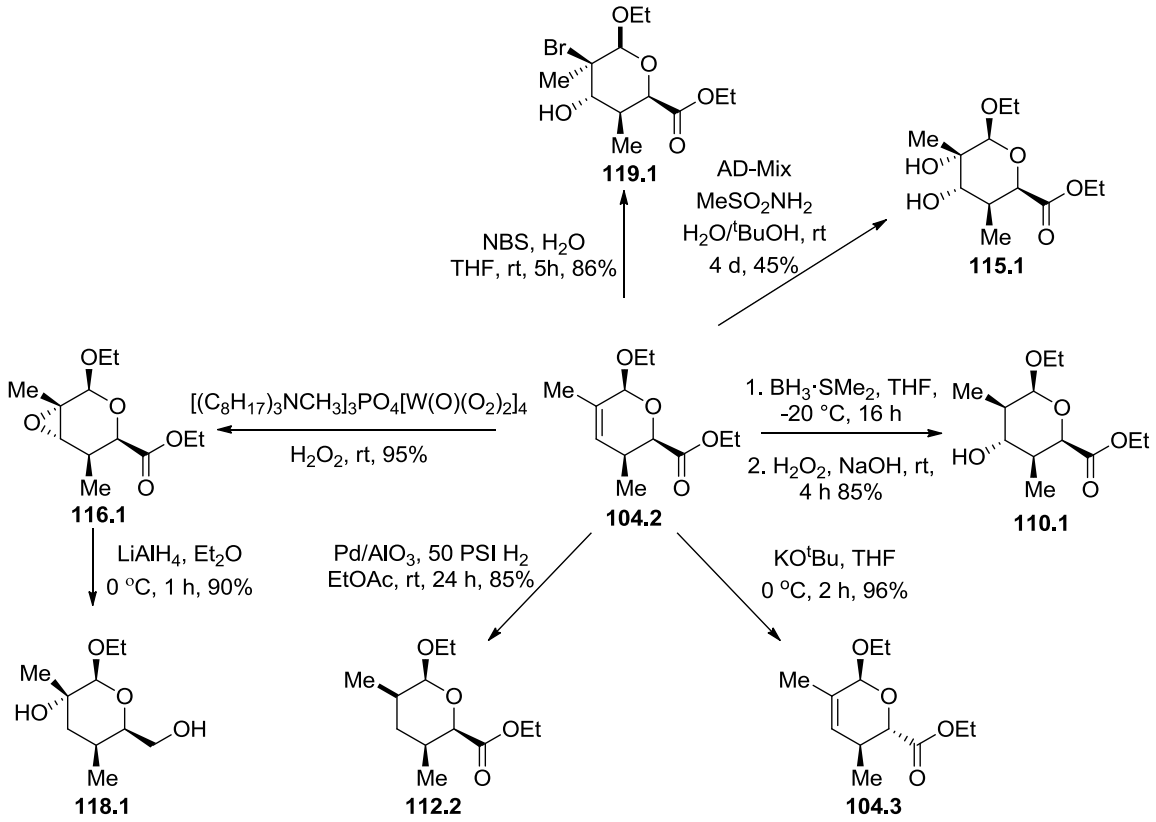
Scheme 145. Diene synthesis

These dienes have been shown to be active in HDA chemistry with the reaction proceeding with good enantiomeric and diastereoselective control around the dihydropyran ring, using a titanium-BINOL catalyst developed by Mikami *et al.*



Scheme 146. Enantioselective synthesis of dihydropyran **18.2**

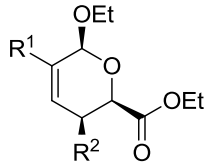
A series of stereoselective derivatisation reactions were then conducted on pyran **104.2** including, hydroboration, hydrogenation, epoxidation, dihydroxylation and epimerization to afford a range of complex enantiomerically pure pyran based building blocks, which are ideally suited for the synthesis of polyketide natural products through a “plug and play” approach. All the performed derivatization reactions proceed with good selectively producing a single diastereomer in good yield. This represents a highly efficient route to the generation of up to five contiguous stereocentres that are a common feature of polyketide natural products (Scheme 147).



Scheme 147. Range of diastereoselective derivatisation reactions of dihydropyran **104.2**

Methodology has also been developed to allow further elaboration of the pyran structure through exploiting the masked aldehyde character of the hemi-acetal, and through utilization of the ester functionality.

This HDA chemistry was also applied to two other diene analogues which gave rise to a new series of mono-methyldihydropyrans **132.2** and **133.1**, which differ in position of their methyl groups around the ring. By gaining access to analogues of this motif, through substitution of the methyl groups for protons, a greater number of potential natural product targets can potentially be reached. Furthermore, this approach could potentially allow for structure activity relationship (SAR) studies to be performed, to help decipher which structural elements within a natural product are responsible for its biological activity, by allowing access to non-natural isomers.



132.2 R^1 = Me, R^2 = H
133.1 R^1 = H, R^2 = Me

Figure 49. Dihydropyran analogues

Experimental

General conditions

Infrared spectra (4000 cm^{-1} to 650 cm^{-1}) were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a Universal ATR accessory for sampling. The machine has internal calibration and only selected peaks are quoted in *ν* (wavenumbers, cm^{-1}).

Proton magnetic resonance spectra were recorded at 300.22 MHz on a Bruker Avance 300 spectrometer unless otherwise stated. Chemical shifts (δH) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The multiplicities and general assignments of spectroscopic data are denoted as: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), triplet of doublets (td), quartet of doublets (qd), triplet of triplets (tt), multiplet (m), aromatic (Ar), and apparent (app.). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Carbon magnetic resonance spectra were recorded at 75.5 MHz on a Bruker Avance 300 spectrometer unless otherwise stated. Chemical shifts (δC) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) are quoted to the nearest 0.1 Hz.

Mass spectra were recorded on a Bruker Daltonics micrOTOF electrospray time-of-flight (ESITOF) mass spectrometer. Samples were introduced either by syringe pump or flow injection using an auto-sampler. Samples were diluted in either methanol or acetonitrile.

All capillary melting point determinations were carried out using Büchi 535 melting point apparatus and reported to the nearest degree Celsius (° C).

Analytical thin layer chromatography was carried out using commercially available polyethylene backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, p-anisaldehyde or phosphomolybdic acid followed by heating. Flash chromatography was performed under medium pressure using Merck 60 H silica gel (35-75 μm). Samples were loaded as saturated solutions in an appropriate solvent.

Reactions requiring anhydrous conditions were performed under nitrogen in oven-dried apparatus, which was allowed to cool under nitrogen prior to use. Anhydrous solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to the fraction of petroleum ether boiling at

40-60 °C. Ether refers to diethyl ether. Hexanes refer to the hexane fraction of petroleum. Solvents were evaporated on a Büchi Rotorvapor.

All commercially available compounds were used as obtained from the chemical suppliers, unless otherwise stated. All temperatures quoted are external.

General Procedures General Procedure A: *N*-Acetylation of amines

Amine (1.0 mmol) was added to phenylmethylene diacetate **7.2** (0.291 g, 1.5 mmol) the reaction was stirred at 70 °C for 16 h. The crude reaction mixture was then directly purified by column chromatography to give the isolated acetamide. Where the reaction mixture was not homogeneous 2 mL of EtOAc was added at the start of the reaction.

General Procedure B: *O*-Acetylation of alcohols

Alcohol (1.0 mmol) was added to phenylmethylene diacetate **7.2** (0.291 g, 1.5 mmol) and K_2CO_3 (0.270 g, 2.0 mmol) the reaction was stirred at 80 °C for 16 h. the crude reaction mixture was then directly purified by column chromatography to give the isolated ester. Where the alcohol was a solid at 60 °C 2 mL of toluene was added at the start of the reaction.

General Procedure C: Synthesis of acylation reagents

para-Toluenesulphonic acid (mono hydrate) (0.18 g, 0.94 mmol) was added to a mixture of benzladehyde (1.0 g, 9.4 mmol) and anhydride (18.8 mmol) at rt. The reaction was stirred for 12 h and then diluted with Et_2O (50 mL) and washed with saturated Na_2CO_3 (3 x 20 mL). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound which was used in subsequent steps without further purification unless otherwise stated.

General Procedure D: *N*-acylation of amines

Amine (1.0 mmol) was added to the acylation reagent (1.5 mmol) the reaction was stirred at 70 °C for 16 h. the crude reaction mixture was then directly purified by column chromatography to give the isolated amide.

General Procedure E: *O*-acylation of alcohols

Alcohol (1.0 mmol) was added to the acylation reagent (1.5 mmol) and K_2CO_3 (0.270 g, 2.0 mmol). The reaction was stirred at 90 °C for 16 h. The crude reaction mixture was then directly purified by column chromatography to give the isolated ester.

General Procedure F: *N*-formylation of amines

Amine (2.0 mmol) was added to (Formyloxy)(phenyl)methyl acetate **44.2** (0.582 g, 3.0 mmol), the reaction was stirred at rt for 1 h. The crude reaction mixture was then directly purified by column chromatography to give the isolated formamide. Where the reaction mixture was not homogeneous 2 mL of EtOAc was added at the start of the reaction.

General Procedure G: *N*-formylation of α-amino acids

(Formyloxy)(phenyl)methyl acetate **44.2** (0.291 g, 1.5 mmol) was added to a mixture of amino acid (1.0 mmol) and $NaHCO_3$ in H_2O (4 mL). The reaction was stirred at rt for 16 h. The reaction mixture when then made acidic with 1 M HCl and extracted with CH_2Cl_2 (3x 10 mL), the organics were combined, dried ($MgSO_4$) and concentrated *in vacuo.* The residue was then purified *via* recrystallization with EtOAc and petroleum ether to give the isolated formyl carboxylic acid.

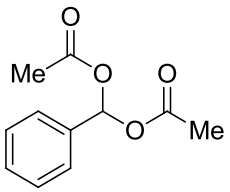
General Procedure H: *O*-formylation of alcohols

Alcohol (1.0 mmol) was added to (Formyloxy)(phenyl)methyl acetate **44.2** (0.291 g, 1.5 mmol) and $NaHCO_3$ (0.168 g, 2.0 mmol), the reaction was stirred at 60 °C for 16 h. The crude reaction mixture was then directly purified by column chromatography to give the isolated formate ester. Where the alcohol was a solid at 60 °C, 2 mL of EtOAc was added at the start of the reaction.

General Procedure I: Acetal synthesis from 1,2- and 1,3-diols

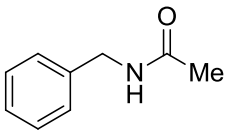
Diol (1.0 mmol) and acetic acid (0.65 µL, 0.01 mmol) were added to phenylmethylene diacetate **7.2** (0.582 g, 3.0 mmol) in MeCN (3 mL) and heated to 40 °C for 12 h. The crude reaction mixture was concentrated under vacuum and the resulting residue was purified by column chromatography to give the isolated acetal.

Phenylmethylene diacetate 7.2



General procedure C was followed to afford the title compound as a clear oil in 98% yield (1.92 g, 9.21 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (s, 1H, C*H*$(OAc)_2$), 7.6 – 7.5 (m, 2H, Ar*H*), 7.5 – 7.4 (m, 3H. Ar*H*), 2.1 (s, 6H, 2 x CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 135.6, 129.9, 128.8, 126.8, 89.8, 21.0. I.R (thinfilm) *v* max (cm^{-1}): 2981 (ArC-H), 1746 (C=O); HRMS (ESI): m/z calculated for $C_{11}H_{12}O_4$: requires: 231.0633 for $[M+Na]^+$; found: 231.0683.

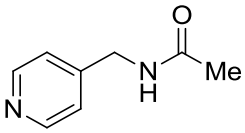
***N*-Benzylacetamide 34a**



General procedure A was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a cream solid in 86% yield (0.128 g, 0.86 mmol). ^{1}H NMR (300 MHz, $CDCl_3$); δ 7.4 – 7.2 (m, 5H, Ar*H*), 5.9 (s, 1H, N*H*), 4.4 (d, *J* = 5.7 Hz, 2H, CH_2), 2.0 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 138.3, 128.8, 128.0, 127.7, 43.9, 23.4.

Analytical data in accordance with literature.[299]

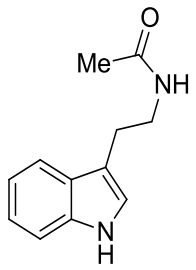
***N*-(pyridin-4-ylmethyl)acetamide 34b**



General procedure A was followed. Eluent 30% EtOAc and 1% NEt_3 in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a orange oil in 84% yield (0.126 g, 0.84 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.6 – 8.5 (m, 2H, Ar*H*), 7.2 – 7.1 (m, 2H, Ar*H*), 6.1 (s, 1H, N*H*), 4.4 (d, *J* = 6.1 Hz, 2H, CH_2), 2.1 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 150.1, 147.5, 122.4, 42.6, 23.3.

Analytical data in accordance with literature.[1]

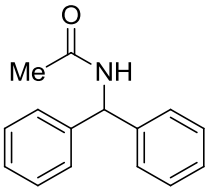
_N_-(2-(1H-indol-3-yl)ethyl)acetamide 34c



General procedure A was followed. Eluent 100% EtOAc, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale brown solid in 62% yield (0.125 g, 0.62 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.2 (s, 1H, N*H*), 7.6 (ddt, *J* = 7.8, 1.5, 0.8 Hz, 1H, Ar*H*), 7.4 (dt, *J* = 8.1, 1.0 Hz, 1H, Ar*H*), 7.2 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, Ar*H*), 7.1 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, Ar*H*), 7.1 – 7.0 (m, 1H, Ar*H*), 5.5 (s, 1H, N*H*), 3.6 (q, *J* = 6.5 Hz, 2H, CH_2CH_2NH), 3.0 (td, *J* = 6.7, 0.9 Hz, 2H, CH_2CH_2NH), 1.9 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 136.5, 127.5, 122.4, 122.2, 119.7, 118.8, 113.1, 111.4, 77.4, 39.9, 25.4, 23.6.

Analytical data in accordance with literature.[300]

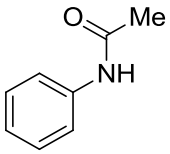
_N_-Benzhydrylacetamide 34d



General procedure A was followed. Eluent 20% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as crystalline white solid in 70% yield (0.158 g, 0.70 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (qt, *J* = 6.2, 1.8 Hz, 5H, Ar*H*), 7.3 (s, 5H, Ar*H*), 6.3 (d, *J* = 8.0 Hz, 1H, C*H*), 6.0 (s, 1H, N*H*), 2.1 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 141.6, 128.8, 127.6, 127.5, 57.1, 23.6.

Analytical data in accordance with literature.[301]

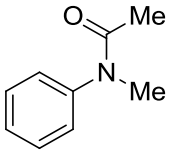
_N_-Phenylacetamide 34e



General procedure A was followed. Eluent 20% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow solid in 68% yield (0.92 g, 0.68 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 – 7.5 (m, 2H, Ar*H*), 7.3 (t, *J* = 7.9 Hz, 2H, Ar*H*), 7.2 – 7.1 (m, 1H, Ar*H*), 2.2 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 138.0, 129.2, 124.5, 119.9, 24.8.

Analytical data in accordance with literature.[299]

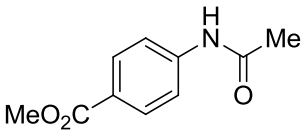
_N_-methyl-_N_-phenylacetamide 34f



General procedure A was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale green solid in 60% yield (0.089 g, 0.60 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (dd, *J* = 8.3, 6.5 Hz, 2H, Ar*H*), 7.4 – 7.3 (m, 1H, Ar*H*), 7.2 – 7.1 (m, 2H, Ar*H*), 3.3 (s, 3H, NCH_3), 1.9 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 144.7, 129.9, 127.8, 127.2, 37.3, 22.6.

Analytical data in accordance with literature.[302]

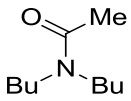
Methyl 4-acetamidobenzoate 34g



General procedure A was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow solid in 65% yield (0.126 g, 0.65 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 – 7.9 (m, 2H, Ar*H*), 7.6 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.4 (s, 1H, N*H*), 3.9 (s, 3H, CO_2CH_3), 2.2 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 166.7, 142.2, 131.0, 125.7, 118.8, 52.2, 25.0.

Analytical data in accordance with literature.[303]

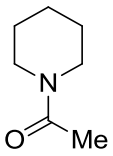
***N,N*-dibutylacetamide 34h**



General procedure A was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 90% yield (0.154 g, 0.90 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.3 – 3.2 (m, 2H, NCH_2), 3.2 – 3.2 (m, 2H, NCH_2), 2.1 (s, 3H, CH_3), 1.5 (dddd, *J* = 15.2, 9.2, 7.8, 5.4 Hz, 4H, $CH_2CH_2CH_2$), 1.3 (hept, *J* = 7.4 Hz, 4H, $CH_2CH_2CH_3$), 0.9 (dt, *J* = 10.0, 7.3 Hz, 6H, 2x CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 48.7, 45.6, 31.1, 30.0, 21.7, 20.4, 20.2, 14.0, 14.0.

Analytical data in accordance with literature.[304]

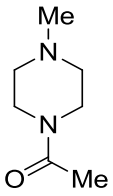
1-(piperidin-1-yl)ethanone 34i



General procedure A was followed. Eluent 20% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 95% yield (0.121 g, 0.95 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.6 – 3.5 (m, 2H, NCH_{AX}), 3.4 (dd, *J* = 6.2, 4.6 Hz, 2H, NCH_{EQ}), 2.1 (s, 3H, CH_3), 1.7 – 1.4 (m, 6H, $CH_2CH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 47.6, 42.6, 26.6, 25.6, 24.6, 21.7.

Analytical data in accordance with literature.[299]

1-(4-methylpiperazin-1-yl)ethanone 34j

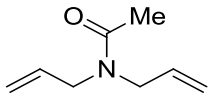


General procedure A was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow in 92% yield (0.131 g, 0.92 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.7 –

3.6 (m, 2H, AcNCH_{AX}), 3.5 – 3.4 (m, 2H, AcNCH_{EQ}), 2.4 (dt, *J* = 10.0, 5.2 Hz, 4H, CH_2NCH$_3$), 2.3 (s, 3H, CH$_2$NCH_3), 2.1 (s, 3H, (C=O)CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 55.2, 54.7, 46.3, 46.1, 41.4, 21.5.

Analytical data in accordance with literature.[305]

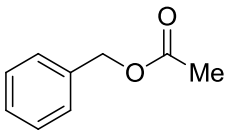
_N,N_-diallylacetamide 34k



General procedure A was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 88% yield (0.122 g, 0.88 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.9 – 5.6 (m, 2H, C*H*=CH$_2$), 5.3 – 5.0 (m, 4H, CH=CH_2), 4.0 (dt, *J* = 6.1, 1.4 Hz, 2H, NCH_aH$_b$), 3.9 (dt, *J* = 4.9, 1.8 Hz, 2H, NCH$_a$$H_b$), 2.1 (s, 3H, C$H_3$).^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 133.4, 132.7, 117.4, 116.7, 50.1, 47.9, 21.5.

Analytical data in accordance with literature.[304]

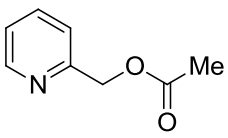
Benzyl acetate 39a



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 90% yield (0.135 g, 0.90 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 – 7.3 (m, 5H, Ar*H*), 5.1 (s, 2H, CH_2Ph), 2.1 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 136.0, 128.7, 128.4, 66.5, 21.2.

Analytical data in accordance with literature.[306]

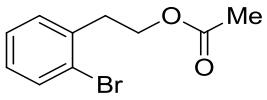
Pyridin-2-ylmethyl acetate 39b



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 70% yield (0.105 g, 0.70 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.6 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H, Ar*H*), 7.7 (td, *J* = 7.7, 1.8 Hz, 1H, Ar*H*), 7.3 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.3 (s, 1H, Ar*H*), 5.2 (s, 2H, CH_2), 2.2 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 155.8, 149.7, 136.9, 123.0, 122.0, 67.0, 21.1.

Analytical data in accordance with literature.[307]

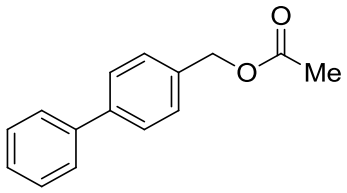
2-Bromophenethyl acetate 39c



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 76% yield (0.184 g, 0.76 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (dt, *J* = 7.9, 0.9 Hz, 1H, Ar*H*), 7.3 – 7.2 (m, 2H, Ar*H*), 7.1 (ddd, *J* = 7.9, 5.1, 4.1 Hz, 1H, Ar*H*), 4.3 (t, *J* = 7.0 Hz, 2H, CH_2OC(O)CH_3), 3.1 (t, *J* = 7.0 Hz, 2H, ArCH_2), 2.0 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 137.3, 133.1, 131.2, 128.5, 127.6, 124.8, 63.5, 35.4, 21.1.

Analytical data in accordance with literature.[308]

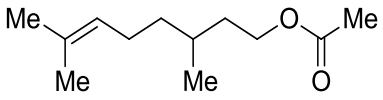
[1,1'-biphenyl]-4-ylmethyl acetate 39d



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 68% yield (0.153 g, 0.68 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 – 7.6 (m, 4H, Ar*H*), 7.5 – 7.4 (m, 4H, Ar*H*), 7.4 – 7.3 (m, 1H, Ar*H*), 5.2 (s, 2H, CH_2), 2.1 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 141.4, 140.8, 135.0, 128.9, 127.6, 127.5, 127.3, 66.2, 21.2.

Analytical data in accordance with literature.[309]

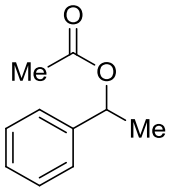
3,7-Dimethyloct-6-en-1-yl acetate 39e



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 90% yield (0.178 g, 0.90 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.1 (tdt, *J* = 5.8, 3.0, 1.5 Hz, 1H, C=C*H*), 4.2 – 4.0 (m, 2H, CH_2OAc), 2.0 (s, 3H, (C=O)CH_3), 2.0 (dt, *J* = 15.0, 7.7 Hz, 2H, CH_2), 1.7 – 1.6 (m, 4H, CH_2), 1.6 (d, *J* = 1.4 Hz, 3H,CH_3(C)CH_3), 1.6 – 1.3 (m, 3H, CH_3(C)CH_3), 1.2 (dddd, *J* = 13.5, 9.1, 7.5, 6.2 Hz, 1H, (C*H*CH_3), 0.9 (d, *J* = 6.4 Hz, 3H, CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 131.5, 124.7, 63.2, 37.1, 35.5, 29.6, 25.9, 25.5, 21.2, 19.5, 17.8.

Analytical data in accordance with literature.[307]

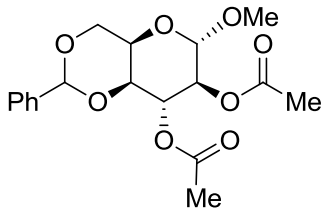
(rac)-1-phenylethyl acetate 39f



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 77% yield (0.126 g, 0.77 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 5H, Ar*H*), 5.9 (q, *J* = 6.6 Hz, 1H, C*H*), 2.1 (s, 3H, C(O)CH_3), 1.5 (d, *J* = 6.6 Hz, 3H, CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 141.8, 128.6, 128.0, 126.2, 72.5, 22.4, 21.5.

Analytical data in accordance with literature.[310]

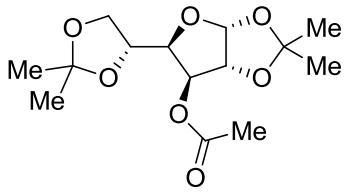
(4a*R*,6*S*,7*S*,8*R*,8a*S*)-6-Methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diyl diacetate 39g



(4a*R*,6*S*,7*S*,8*S*,8a*R*)-6-Methoxy-2-phenylhexahydropyrano[3,2-d][1,3]dioxine-7,8-diol (0.282 g, 1.0 mmol) was added to phenylmethylene diacetate (0.582 g, 3.0 mmol) and K_2CO_3 (0.270 g, 2.0 mmol) the reaction was stirred at 90 °C for 16 h. The crude reaction mixture was then directly purified by column chromatography to give the title compound. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 65% yield (0.238 g, 0.65 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (qd, *J* = 5.4, 4.5, 1.9 Hz, 2H, Ar*H*), 7.4 (dt, *J* = 4.6, 2.8 Hz, 3H, Ar*H*), 5.6 (t, *J* = 9.6 Hz, 1H, C*H*OCH_3), 5.5 (s, 1H, PhC*H*), 5.0 – 4.8 (m, 2H, 2 x C*H*C(O)CH_3), 4.3 (dd, *J* = 10.1, 4.7 Hz, 1H, CH_2CH(O)C*H*(O)), 3.9 (td, *J* = 9.9, 4.7 Hz, 1H, CH_2C*H*(O)CH(O)), 3.8 (t, *J* = 10.2 Hz, 1H, OC$H_a$$H_b$CHO), 3.6 (t, *J* = 9.6 Hz, 1H, OC$H_a$$H_b$CHO), 3.4 (s, 3H, OC$H_3$), 2.1 (s, 3H, C(O)C$H_3$), 2.1 (s, 3H, C(O)C$H_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.9, 137.0, 129.2, 128.4, 126.3, 101.7, 97.7, 79.3, 71.7, 69.1, 69.0, 62.4, 55.5, 21.0, 20.9.

Analytical data in accordance with literature.[311]

(3a*R*,5*R*,6*S*,6a*R*)-5-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl acetate 39h

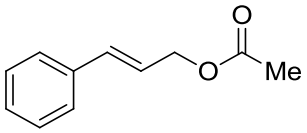


General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 70% yield (0.21 g, 0.69 mmol). $[\alpha]_D^{20}$ = -32 in $CHCl_3$. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.9 (d, *J* = 3.7 Hz, 1H, OC*H*O), 5.2 (d, *J* = 2.4 Hz, 1H, OC*H*CHOC(O)CH_3), 4.5 (d, *J* = 3.7 Hz, 1H, OC*H*C(O)CH_2), 4.3 – 4.2 (m, 2H, OCH(CHOCH_2O)C(O)CH_3 and C*H*C(O)CH_3), 4.1 (tdd, *J* = 10.7, 7.0, 3.3 Hz, 2H, OCH_2CHO), 2.1 (s, 3H, CHC(O)CH_3), 1.5 (s, 3H,

OCO(C*H*$_{3a}$CH$_{3b}$)), 1.4 (s, 3H, OCO(CH$_{3a}$C*H*$_{3b}$)), 1.3 (s, 3H, OCO(C*H*$_{3a}$CH$_{3b}$)), 1.3 (s, 3H, OCO(CH$_{3a}$C*H*$_{3b}$)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 112.4, 109.5, 105.1, 83.4, 79.8, 76.3, 72.5, 67.3, 27.0, 26.8, 26.3, 25.4, 21.1.

Analytical data in accordance with literature.[312]

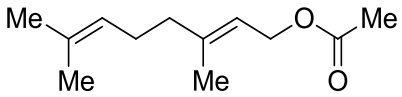
Cinnamyl acetate 39i



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 83% yield (0.146 g, 0.83 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (s, 5H, Ar*H*), 6.7 (dt, *J* = 15.9, 1.4 Hz, 1H, CH=C*H*CH$_2$), 6.3 (dt, *J* = 15.9, 6.5 Hz, 1H, C*H*=CHCH$_2$), 4.7 (dd, *J* = 6.5, 1.4 Hz, 2H, CH=CHC*H*$_2$), 2.1 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 136.3, 134.4, 128.7, 128.2, 126.7, 123.3, 65.2, 21.2.

Analytical data in accordance with literature.[313]

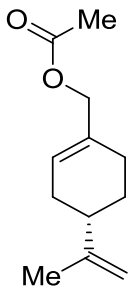
(*E*)-3,7-dimethylocta-2,6-dien-1-yl acetate 39j



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a waxy white solid in 89% yield (0.174 g, 0.89 mmol).^{1}H NMR (300 MHz, $CDCl_3$) δ 5.3 (tq, *J* = 7.2, 1.3 Hz, 1H, C=C*H*CH$_2$O), 5.1 (tq, *J* = 5.5, 1.5 Hz, 1H, C=C*H*CH$_2$), 4.6 (d, *J* = 7.1 Hz, 2H, C*H*$_2$OAc), 2.2 – 2.0 (m, 7H, 2 x C*H*$_2$ and (C=O)C*H*$_3$), 1.7 (dd, *J* = 5.9, 1.3 Hz, 6H, C*H*$_3$(C)C*H*$_3$), 1.6 (d, *J* = 1.4 Hz, 3H, CH$_2$C(C*H*$_3$)=CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 142.5, 132.0, 123.9, 118.3, 61.6, 39.7, 26.4, 25.8, 21.2, 17.8, 16.6.

Analytical data in accordance with literature.[307]

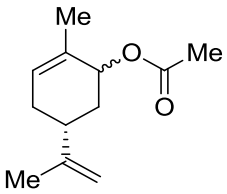
(*S*)-(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl acetate 39k



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 85% yield (0.165 g, 0.85 mmol). $[\alpha]_D^{20}$ = -65.5 in $CHCl_3$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8 (dd, *J* = 4.6, 2.4 Hz, 1H, CH_2C=C*H*), 4.8 – 4.7 (m, 2H, C=CH_2), 4.5 (d, *J* = 1.7 Hz, 2H, CH_2OAc), 2.2 – 2.0 (m, 7H, 2 x CH_2 and (C=O)CH_3), 2.0 – 1.8 (m, 2H, CH_2), 1.7 (t, *J* = 1.1 Hz, 3H, CH_3C=CH_2), 1.5 – 1.4 (m, 1H, C*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 149.8, 132.7, 126.0, 108.9, 68.7, 40.9, 30.6, 27.4, 26.5, 21.2, 20.9.

Analytical data in accordance with literature.[314]

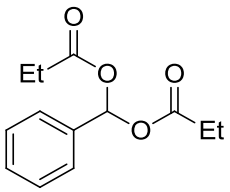
2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl acetate (mix of isomers) **39l**



General procedure B was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 68% yield (0.132 g, 0.68 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.7 (dt, *J* = 5.3, 1.8 Hz, 1H), 5.6 (dq, *J* = 5.5, 1.8 Hz, 1H), 5.4 (d, *J* = 1.5 Hz, 1H), 5.3 – 5.2 (m, 1H), 4.8 – 4.7 (m, 4H), 2.4 – 2.1 (m, 4H), 2.1 (d, *J* = 1.0 Hz, 6H), 2.0 – 1.8 (m, 3H), 1.7 (dt, *J* = 4.4, 1.1 Hz, 5H), 1.7 (dd, *J* = 2.7, 1.4 Hz, 3H), 1.6 (dp, *J* = 2.5, 1.3 Hz, 3H), 1.6 – 1.5 (m, 1H), 1.5 – 1.4 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.1, 148.9, 148.4, 133.0, 131.1, 128.1, 126.1, 109.5, 109.3, 73.4, 70.8, 40.4, 35.9, 34.1, 33.7, 31.0, 30.9, 21.6, 21.4, 21.0, 20.8, 20.6, 19.0.

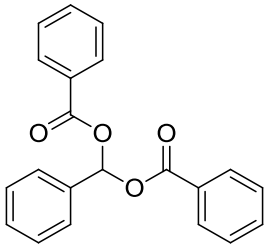
Analytical data in accordance with literature.[315]

Phenylmethylene dipropionate 41a



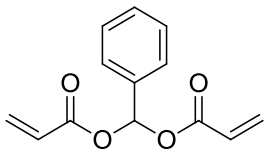
General procedure C was followed to afford the title compound as a clear oil in 97% yield (2.15 g, 9.12 mmol).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (s, 1H, C*H*$(OCOEt)_2$), 7.5 (qd, *J* = 3.8, 1.5 Hz, 2H, Ar*H*), 7.4 (ddt, *J* = 4.3, 3.1, 1.6 Hz, 3H, Ar*H*), 2.5 – 2.3 (m, 4H, 2 x CH_2CH_3), 1.2 (dt, *J* = 8.5, 7.5 Hz, 6H, 2 x CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 170.4, 135.8, 129.8, 128.7, 126.8, 89.7, 28.9, 27.5, 8.9, 8.5. I.R (thinfilm) *v* max (cm^{-1}): 2983 (ArC-H), 1756 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{12}O_4$: requires: 259.0946 for $[M+Na]^+$; found: 259.0995.

Phenylmethylene dibenzoate 41b



General procedure C was followed to afford the title compound as a clear oil in 99% yield (3.09 g, 9.30 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.3 – 8.1 (m, 5H, C*H* and Ar*H*), 7.8 – 7.6 (m, 3H, Ar*H*), 7.6 – 7.5 (m, 4H, Ar*H*), 7.5 – 7.4 (m, 4H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 162.5, 134.7, 133.7, 130.7, 130.2, 129.9, 129.2, 129.0, 128.9, 128.6, 126.9, 90.8. I.R (thinfilm) *v* max (cm^{-1}): 3064 (ArC-H), 1722 (C=O); HRMS (ESI): m/z calculated for $C_{21}H_{16}O_4$: requires: 355.0946 for $[M+Na]^+$; found: 355.0929.

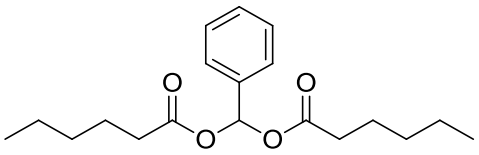
Phenylmethylene diacrylate 41c



General procedure C was followed to afford the title compound as a clear oil in 97% yield (2.12 g, 9.12 mmol). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.9 (s, 1H, C*H*Ph), 7.7 – 7.5 (m, 2H, Ar*H*), 7.5 – 7.4 (m, 3H, Ar*H*), 6.5 (dd, *J* = 17.3, 1.4 Hz, 2H, CH_aH_b=CH), 6.3 – 6.0 (m, 2H, CH_aH_b=C*H*),

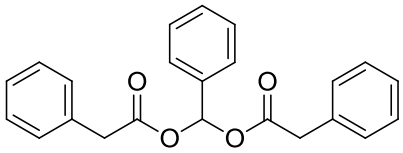
5.9 (dd, *J* = 10.5, 1.3 Hz, 2H, CH_aH_b=CH). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 164.0, 134.8, 132.8, 129.9, 128.8, 127.6, 126.8, 90.1. I.R (thinfilm) *v* max (cm^{-1}): 3040 (ArC-H), 1732 (C=O); HRMS (ESI): m/z calculated for $C_{13}H_{12}O_4$: requires: 255.0633 for $[M+Na]^+$; found: 255.0667.

Phenylmethylene dihexanoate 41d



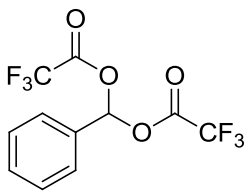
General procedure C was followed to afford the title compound as a clear oil in 96% yield (2.89 g, 9.02 mmol).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (s, 1H, C*H*Ph), 7.5 – 7.5 (m, 2H, Ar*H*), 7.5 – 7.3 (m, 3H, Ar*H*), 2.4 (td, *J* = 7.4, 2.3 Hz, 4H, 2 x (C=O)CH_2CH$_2$), 1.7 – 1.6 (m, 4H, 2 x (C=O)CH$_2$CH_2), 1.3 (dtq, *J* = 10.4, 7.0, 3.1 Hz, 8H, 2 x CH_2CH_2CH$_3$), 0.9 – 0.9 (m, 6H, 2 x CH$_2$CH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 135.9, 129.8, 128.7, 126.8, 89.6, 35.4, 34.2, 31.3, 24.5, 22.4, 14.0. I.R (thinfilm) *v* max (cm^{-1}): 2956 (ArC-H), 1752 (C=O); HRMS (ESI): m/z calculated for $C_{19}H_{28}O_4$: requires: 343.1885 for $[M+Na]^+$; found: 343.1898.

Phenylmethylene bis(2-phenylacetate) 41e



General procedure C was followed to afford the title compound as a clear oil in a 94% yield (3.18 g, 8.84 mmol). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.7 (s, 1H, C*H*Ph), 7.4 – 7.2 (m, 15H, Ar*H*), 3.6 (s, 4H, 2 x CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 135.3, 133.2, 129.9, 129.5, 129.4, 128.7, 127.4, 126.7, 90.3, 41.1. I.R (thinfilm) *v* max (cm^{-1}): 3032, 2981 (ArC-H), 1759 (C=O); HRMS (ESI): m/z calculated for $C_{23}H_{20}O_4$: requires: 383.1259 for $[M+Na]^+$; found: 383.1259.

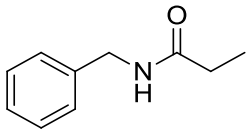
Phenylmethylene bis(2,2,2-trifluoroacetate) 41f



To a solution of benzaldehyde (0.50 g, 4.7 mmol) and trifluoroacetic anhydride (0.98 mL, 7.08 mmol) was added trifluoroacetic acid (0.035 mL, 0.47 mmol) dropwise at rt. After 2 h the

reaction was concentrated *en vacuo* to give the title compound as a yellow oil in 95% yield (1.4 g, 4.5 mmol). Taken forward to be used in subsequent steps without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 (s, 1H, Ar*H*), 7.6 (dd, *J* = 7.8, 1.9 Hz, 2H, Ar*H*), 7.6 – 7.5 (m, 3H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3 (q, ^{2}*J*C-F = 44.7 Hz), 134.4, 131.8, 129.4, 127.0, 114.1 (q, ^{1}*J*C-F = 285.5 Hz), 93.8. I.R (thinfilm) *v* max (cm^{-1}): 1809 (C=O)

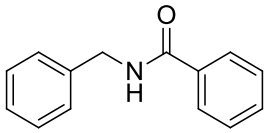
_N_-benzylpropionamide 42a



General procedure D was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a fluffy white solid in 95% yield (0.155 g, 0.95 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.2 (m, 5H, Ar*H*), 5.8 (s, 1H, N*H*), 4.4 (d, *J* = 5.7 Hz, 2H, CH_2Ph), 2.2 (q, *J* = 7.6 Hz, 2H, CH_2CH$_3$), 1.2 (t, *J* = 7.6 Hz, 3H, CH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 138.5, 128.8, 128.0, 127.6, 43.7, 29.8, 10.0.

Analytical data in accordance with literature.[316]

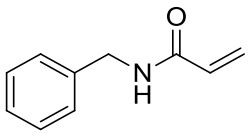
_N_-benzylbenzamide 42b



General procedure D was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a cream solid in 87% yield (0.184 g, 0.87 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8 – 7.7 (m, 2H, Ar*H*), 7.6 – 7.3 (m, 8H, Ar*H*), 6.4 (s, 1H, N*H*), 4.7 (d, *J* = 5.6 Hz, 2H. CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 138.3, 134.5, 131.7, 129.0, 128.8, 128.1, 127.8, 127.1, 44.3.

Analytical data in accordance with literature.[316]

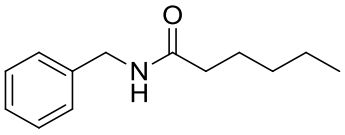
_N_-benzylacrylamide 42c



General procedure D was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a cream solid in 96% yield (0.154 g, 0.96 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 5H, Ar*H*), 6.3 (dd, *J* = 16.9, 1.5 Hz, 1H, C*H*=CH$_a$H$_b$), 6.1 (dd, *J* = 17.0, 10.2 Hz, 1H, CH=C*H*$_a$H$_b$), 5.9 (s, 1H, N*H*), 5.7 (dd, *J* = 10.2, 1.5 Hz, 1H, CH=CH$_a$*H*$_b$), 4.5 (d, *J* = 5.8 Hz, 2H, C*H*$_2$Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 138.1, 130.7, 128.9, 128.7, 128.7, 128.1, 128.0, 127.8, 127.0, 126.8, 43.8.

Analytical data in accordance with literature.[317]

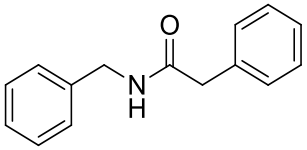
_N_-benzylhexanamide 42d



General procedure D was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 91% yield (0.186 g, 0.91 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 5H, Ar*H*), 5.7 (s, 1H, N*H*), 4.4 (d, *J* = 5.7 Hz, 2H, C*H*$_2$Ph), 2.2 (dd, *J* = 8.6, 6.7 Hz, 2H, (C=O)C*H*$_2$CH$_2$CH$_2$), 1.7 – 1.6 (m, 2H, (C=O)CH$_2$C*H*$_2$CH$_2$), 1.3 (dq, *J* = 7.2, 3.8, 3.2 Hz, 4H, (C=O)CH$_2$CH$_2$C*H*$_2$C*H*$_2$), 0.9 – 0.8 (m, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 138.5, 128.9, 128.0, 127.7, 43.7, 37.0, 31.6, 25.6, 22.6, 14.1.

Analytical data in accordance with literature.[318]

_N_-benzyl-2-phenylacetamide 42e

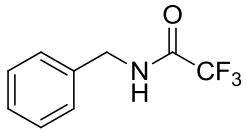


General procedure D was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the

title compound as a pale brown solid in a 79% yield (0.178 g, 0.79 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3 (s, 8H, Ar*H*), 7.2 – 7.1 (m, 2H, Ar*H*), 5.7 (s, 1H, N*H*), 4.4 (d, *J* = 5.8 Hz, 2H, PhCH_2NH), 3.6 (s, 2H, PhCH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 138.2, 134.9, 129.6, 129.2, 128.8, 127.6, 127.6, 44.0, 43.7.

Analytical data in accordance with literature.[318]

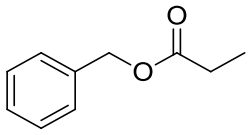
N-benzyl-2,2,2-trifluoroacetamide 42f



Benzylamine (0.107 g, 1.0 mmol) was added to phenylmethylene bis(2,2,2-trifluoroacetate) (0.474 g, 1.5 mmol) the reaction was stirred at rt for 1 h. the crude reaction mixture was then directly purified by column chromatography to give the isolated title product. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 91% yield (0.184 g, 0.91 mmol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 3H, Ar*H*), 7.32 – 7.27 (m, 2H, Ar*H*), 6.6 (s, 1H, N*H*), 4.5 (d, *J* = 5.8 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3 (q, ^{2}JC-F = 37.2 Hz), 135.9, 129.1, 128.4, 128.1, 116.0 (q, ^{1}JC-F = 287.8 Hz), 44.0.

Analytical data in accordance with literature.[319]

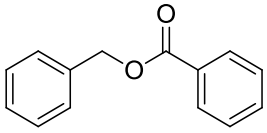
Benzyl propionate 43a



General procedure E was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 94% yield (0.154 g, 0.94 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 5H, Ar*H*), 5.1 (s, 2H, CH_2Ph), 2.4 (q, *J* = 7.6 Hz, 2H, CH_2CH$_3$), 1.2 (t, *J* = 7.6 Hz, 3H, CH$_2$CH_3). C NMR (75 MHz, $CDCl_3$) δ 174.5, 136.3, 128.7, 128.3, 126.8, 66.3, 27.8, 9.3.

Analytical data in accordance with literature.[320]

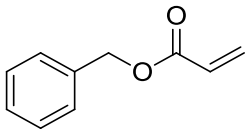
Benzyl benzoate 43b



General procedure E was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 78% yield (0.166 g, 0.78 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.2 – 7.9 (m, 2H, Ar*H*), 7.6 – 7.5 (m, 1H, Ar*H*), 7.5 – 7.3 (m, 7H, Ar*H*), 5.4 (s, 2H, CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 136.2, 133.2, 130.3, 129.8, 128.7, 128.5, 128.4, 128.3, 66.8.

Analytical data in accordance with literature.[320]

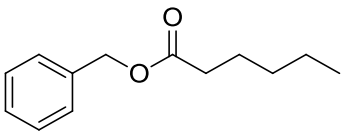
Benzyl acrylate 43c



General procedure E was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 81% yield (0.131 g, 0.81 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 5H, Ar*H*), 6.5 (dd, *J* = 17.3, 1.4 Hz, 1H, C*H*=CH_aH_b), 6.2 (dd, *J* = 17.3, 10.4 Hz, 1H, CH=C*H*$_a$H$_b$), 5.9 (dd, *J* = 10.4, 1.4 Hz, 1H, CH=CH_a*H*$_b$), 5.2 (s, 2H, CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 136.0, 131.2, 128.7, 128.5, 128.4, 128.4, 66.5.

Analytical data in accordance with literature.[320]

Benzyl hexanoate 43d

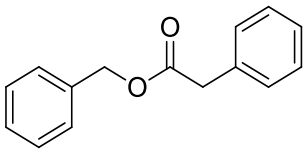


General procedure E was followed. Eluent 3% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 70% yield (0.144 g, 0.70 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 5H, Ar*H*), 5.1 (s, 2H, CH_2Ph), 2.4 (t, *J* = 7.5 Hz, 2H, (C=O)CH_2CH$_2$CH$_2$CH$_2$CH$_3$), 1.7 – 1.6 (m, 2H, (C=O)CH$_2$CH_2CH$_2$CH$_2$CH$_3$), 1.3 (dq, *J* = 7.5, 3.8, 3.2 Hz, 4H, (C=O)CH$_2$CH$_2$CH_2CH_2CH$_3$), 0.9 –

0.8 (m, 3H, (C=O)$CH_2CH_2CH_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 136.3, 128.7, 128.3, 126.8, 66.2, 34.4, 31.4, 24.8, 22.4, 14.0.

Analytical data in accordance with literature.[321]

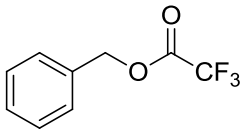
Benzyl 2-phenylacetate 43e



General procedure E was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 62% yield (0.140 g, 0.62 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 – 7.3 (m, 10H, Ar*H*), 5.2 (s, 2H, PhCH_2O), 3.7 (s, 2H, (C=O)CH_2Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 136.0, 134.0, 129.4, 128.7, 128.7, 128.3, 128.2, 127.2, 66.7, 41.5.

Analytical data in accordance with literature.[321]

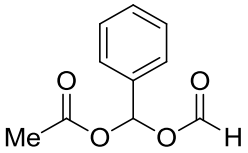
Benzyl 2,2,2-trifluoroacetate 43f



Benzyl alcohol (0.108 g, 1.0 mmol) was added to phenylmethylene bis(2,2,2-trifluoroacetate) (0.474 g, 1.5 mmol) and K_2CO_3 (2.0 mmol, 0.270 g) the reaction was stirred at rt for 1 h. the crude reaction mixture was then directly purified by column chromatography to give the isolated title compound. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 89% yield (0.181 g, 0.89 mmol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4 (s, 5H), 5.4 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5 (q, ^2JC-F = 42.5 Hz), 133.4, 129.4, 129.0, 128.8, 114.6 (q, ^1JC-F = 285.8 Hz), 69.7.

Analytical data in accordance with literature.[322]

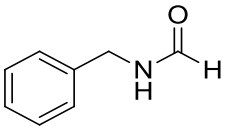
(formyloxy)(phenyl)methyl acetate 44.2



Copper(II) tetrafluoroborate hydrate (0.044 g, 1.80 mmol) was added to a mixture of benzladehyde (2.0 g, 18.0 mmol) and acetic formic anhydride (2.40 g, 27.0 mmol) at -20 °C and stirred for 5 min. The reaction was then quenched with saturated Na_2CO_3 (10 mL) and diluted with Et_2O (50 mL). The reaction was then washed with saturated Na_2CO_3 (3 x 20 mL). The organics were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5% EtOAc in pet ether Rf = 0.56) to give the title compound as a clear oil in 59% yield.

^{1}H NMR (300MHz, $CDCl_3$) δ = 8.12 (d, *J* = 0.9 Hz, 1H, (C=O)*H*), 7.77 (s, 1H, C*H*Ar), 7.59 - 7.50 (m, 2H, Ar*H*), 7.47 - 7.41 (m, 3H, Ar*H*), 2.16 (s, 3H, CH_3), ^{13}C NMR (75MHz, $CDCl_3$) δ = 168.8, 158.7, 134.7, 130.0, 128.7, 126.7, 89.2, 20.8, I.R (thinfilm) *v* max (cm^{-1}): 3040 (ArC-H), 1750, 1732 (C=O); HRMS (ESI): m/z calculated for $C_{10}H_{10}O_4$: requires: 217.0471 for $[M+Na]^+$; found: 217.0479.

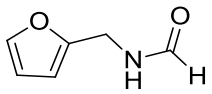
***N*-benzylformamide 47a**



General procedure F was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as an off-white solid in 89% yield (0.24 g, 1.78 mmol). m.p. 60-61 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1 H, (C=O)*H*) (major), 8.00 (d, *J* = 11.9 Hz, 1H, (C=O)*H*) (minor), 7.34 - 7.06 (m, 5H, Ar*H*), 6.38 (br. s., 1H, N*H*), 4.34 (d, *J* = 6.0 Hz, 2H, CH_2NH) (major), 4.27 (d, *J* = 6.6 Hz, 2H, CH_2NH) (minor). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (minor), 161.1 (major), 137.5, 128.8 (minor), 128.6 (major), 127.8 (minor), 127.6 (major), 127.5 (major), 126.8 (minor), 45.5 (minor), 42.0 (major).

Analytical data in accordance with literature.[80]

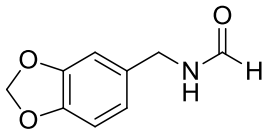
***N*-(furan-2-ylmethyl)formamide 47b**



General procedure F was followed Eluent 25% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 80% yield (0.20 g, 1.60 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H, (C=O)*H*) (major), 8.16 (d, *J* = 11.9 Hz, 1H, (C=O)*H*) (minor), 7.38 (dd, *J* = 0.8, 1.8 Hz, 1H, CHC(*H*)O) (minor), 7.35 (dd, *J* = 0.8, 1.9 Hz, 1H, CHC(*H*)O) (major), 6.32 (dd, *J* = 1.8, 3.3 Hz, 1H, C*H*C(H)O)), 6.24 (dd, *J* = 0.8, 3.2 Hz, 1H, CC*H*), 4.46 (d, *J* = 5.7 Hz, 2H, CH_2NH) (major), 4.36 (d, *J* = 6.4 Hz, 2H, CH_2NH) (minor). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6 (minor), 160.9 (major), 150.5, 142.8 (minor), 142.3 (major), 110.4, 107.6 (major), 107.4 (minor), 38.8 (minor), 34.9 (major).

Analytical data in accordance with literature.[323]

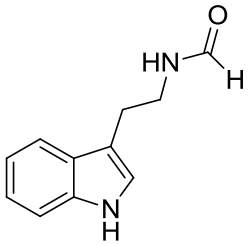
***N*-(benzo[d][1,3]dioxol-5-ylmethyl)formamide 47c**



Gerneral procedure F was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as an off-white crystalline solid in 82% yield (0.293 g, 1.64 mmol). m.p. 96-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H, (C=O)*H*) (major), 8.12 (d, *J* = 12.1 Hz, 1H, (C=O)*H*) (minor), 6.79 - 6.66 (m, 3H, ArH), 6.18 (br. s., 1H, N*H*), 5.96 (s, 2H, OCH_2O) (minor), 5.93 (s, 2H, OCH_2O) (major), 4.35 (d, *J* = 5.8 Hz, 2H, CH_2NH) (major), 4.29 (d, *J* = 6.4 Hz, 2H, CH_2NH) (minor). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5 (minor), 161.0 (major), 147.9, 147.0, 131.4, 121.0 (major), 120.3 (minor), 108.4 (minor), 108.3 (major), 108.2 (major), 107.4 (minor), 101.2 (minor), 101.0 (major), 45.5 (minor), 41.9 (major).

Analytical data in accordance with literature.[299]

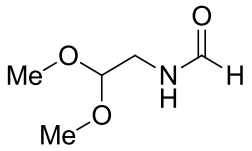
_N_-(2-(1H-indol-3-yl)ethyl)formamide 47d



General procedure F was followed. Eluent 100% EtOAc the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as pale brown viscous oil in 90% yield (0.339 g, 1.80 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (br. s., 1 H, ArN*H*), 8.05 (s, 1 H, (C=O)*H*) (major), 7.84 (d, *J* = 12.1 Hz, 1 H, (C=O)*H*) (minor), 7.60 (d, *J* = 7.9 Hz, 1 H, Ar*H*) (major), 7.56 (d, *J* = 7.9 Hz, 1 H, Ar*H*) (minor), 7.37 (d, *J* = 8.1 Hz, 1 H, Ar*H*), 7.28 - 7.09 (m, 3 H, Ar*H*), 7.01 (d, *J* = 2.1 Hz, 1 H, Ar*H*NH) (major), 6.96 (d, *J* = 2.3 Hz, 1 H, Ar*H*NH) (minor), 5.80 (br. s., 1 H, CH_2N*H*), 3.63 (q, *J* = 6.5 Hz, 2 H, C*H*$_2$NH) (major), 3.48 (q, *J* = 6.5 Hz, 2 H, C*H*$_2$NH) (minor), 3.02 - 2.90 (app m, 2 H, C*H*$_2$CH$_2$NH) (major and minor). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (minor), 161.3 (major), 136.4 (minor), 136.3 (major), 127.1 (major), 126.7 (minor), 122.8 (minor), 122.2 (major), 122.2 (minor), 122.1 (major), 119.4 (minor), 119.4 (major), 118.5 (major), 118.3 (minor), 112.2 (major), 111.5 (minor), 111.3 (major), 111.2 (minor), 41.9 (minor), 38.3 (major), 27.2 (minor), 25.0 (major).

Analytical data in accordance with literature.[299]

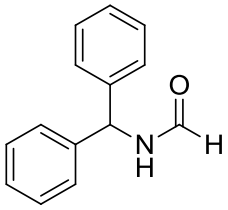
_N_-(2,2-dimethoxyethyl)formamide 47e



General procedure F was followed. Eluent 20% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 95% yield (0.253 g, 1.9 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H, (C=O)*H*) (major), 8.02 (d, *J* = 12.1 Hz, 1H, (C=O)*H*) (minor), 6.03 (br. s., 1H, N*H*), 4.39 (t, *J* = 5.2 Hz, 1H, C*H*(OMe)$_2$) (major), 4.31 (t, *J* = 5.2 Hz, 1H, C*H*(OMe)$_2$) (minor), 3.46 - 3.41 (m, 2H C*H*$_2$NH) (major), 3.40 (s, 6H, OC*H*$_3$) (minor), 3.39 (s, 6H, OC*H*$_3$) (major), 3.29 (dd, *J* = 5.1, 6.6 Hz, 2H, C*H*$_2$NH) (minor). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9 (minor), 161.3 (major), 103.4 (minor), 102.3 (major), 54.7 (minor), 54.4 (major), 43.6 (minor), 39.4 (major). I.R (thinfilm) *v* max (cm^{-1}):

3295 (N-H), 1658 (C=O); HRMS (ESI): m/z calculated for $C_5H_{11}NO_3$: requires: 134.0817 for $[M+H]^+$; found: 134.0824.

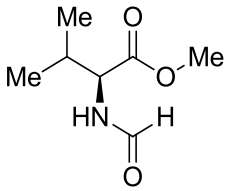
_N_-benzhydrylformamide 47f



General procedure F was followed. Eluent 20% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as an off-white crystalline solid in 83% yield (0.35 g, 1.66 mmol). m.p. 133-134 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H, (C=O)*H*) (major), 8.21 (d, *J* = 11.9 Hz, 1H, (C=O)*H*) (minor), 7.39 - 7.27 (m, 5H, Ar*H*), 7.27 - 7.19 (m, 5H, Ar*H*), 6.33 (d, *J* = 8.3 Hz, 1H, ArC*H*) (major), 6.25 (br. s., 1H, N*H*), 5.77 (d, *J* = 8.3 Hz, 1H, ArC*H*) (minor). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 140.8, 128.9 (minor), 128.7 (major), 128.0 (minor), 127.6 (major), 127.3 (major), 127.2 (minor), 55.6.

Analytical data in accordance with literature.[299]

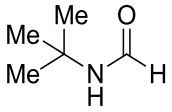
(_S_)-methyl 2-formamido-3-methylbutanoate 47g



General procedure F was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale pink crystalline solid in 93% yield (0.296 g, 1.86 mmol). m.p. 68-69 °C; $[\alpha]_D^{20}$ = -22 in EtOH; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H, (C=O)*H*) (major), 7.98 (d, *J* = 11.7 Hz, 1H, (C=O)*H*) (minor), 6.53 (br. s., 1H, N*H*), 4.62 (ddd, *J* = 0.8, 4.9, 9.1 Hz, 1H, C*H*NH) (major), 3.91 (dd, *J* = 5.1, 10.2 Hz, 1H, C*H*NH) (minor), 3.74 (s, 3H, OCH_3) (minor), 3.72 (s, 3H, OCH_3) (major), 2.23 - 2.08 (m, 1H, C*H*$(CH_3)_2$), 0.93 (d, *J* = 6.8 Hz, 3H, CH(CH_3)$_2$), 0.88 (d, *J* = 6.8 Hz, 3H, CH(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (major), 171.3 (minor), 163.9 (minor), 161.0 (major), 60.3 (minor), 55.5 (major), 52.4 (minor), 52.2 (major), 31.3 (minor), 31.1 (major), 19.0 (minor), 18.8 (major), 17.5 (major), 17.0 (minor)

Analytical data in accordance with literature.[87]

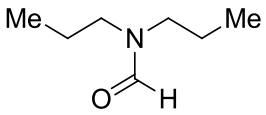
_N_-tert-butylformamide 47h



General procedure F was followed. Eluent 20% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 53% yield (0.107 g, 1.06 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 12.4 Hz, 1H, (C=O)*H*) (minor), 8.03 (s, 1H, (C=O)*H*) (major), 6.15 (br. s., 1H, N*H*) (minor), 5.40 (br. s., 1H, N*H*) (major), 1.38 (s, 9H, CH_3) (minor), 1.33 (s, 9H, CH_3) (major). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (major), 160.6 (minor), 51.3 (major), 50.3 (minor), 30.8 (major), 28.9 (minor).

Analytical data in accordance with literature.[323]

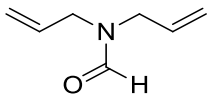
_N,N_-dipropylformamide 47i



General procedure F was followed. Eluent 20% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 74% yield (0.191 g, 1.48 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H, (C=O)*H*), 3.27 - 3.19 (m, 2H, C*H*$_2$CH$_2$CH$_3$), 3.15 (t, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_2$CH$_3$), 1.63 - 1.46 (m, 4H, CH$_2$C*H*$_2$CH$_3$), 0.88 (dt, *J* = 2.2, 7.4 Hz, 6H, C*H*$_2$CH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 49.1, 43.6, 21.7, 20.4, 11.2, 10.8.

Analytical data in accordance with literature.[87]

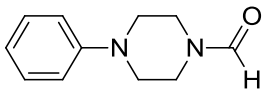
_N,N_-diallylformamide 47j



General procedure F was followed. Eluent 20% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 58% yield (0.145 g, 1.16 mmol). ^{1}H NMR (300 MHz, $CDCl_3$)

δ 8.10 (s, 1H, (C=O)*H*), 5.79 - 5.58 (m, 2H, CH_2CH=CH_2), 5.25 - 5.21 (m, 1H, CH_2CH=CH_aH_b), 5.19 (qd, *J* = 1.3, 4.1 Hz, 1H, CH_2CH=CH_aH_b), 5.17 - 5.14 (m, 2H, CH_2CH=CH_aH_b), 3.91 (td, *J* = 1.3, 5.9 Hz, 2H, CH_2CH=CH_2), 3.79 (td, *J* = 1.2, 5.8 Hz, 2H, CH_2CH=CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 132.9, 131.9, 118.5, 118.0, 49.1, 44.1. I.R (thinfilm) *v* max (cm^{-1}): 1665 (C=O); HRMS (ESI): m/z calculated for $C_7H_{11}NO$: requires: 126.0918 for $[M+H]^+$; found: 126.0932.

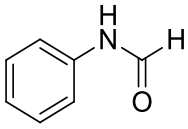
4-phenylpiperazine-1-carbaldehyde 47k



General procedure F was followed. Eluent 30% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale pink crystalline solid in 96% yield (0.365 g, 1.92 mmol). m.p. 83-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H, (C=O)*H*), 7.33 - 7.21 (m, 2H, Ar*H*), 6.97 - 6.87 (m, 3H, Ar*H*), 3.74 - 3.63 (m, 2H $CH_2CH_2NC(O)H$), 3.56 - 3.44 (m, 2H, $CH_2CH_2NC(O)H$), 3.14 (td, *J* = 5.3, 11.1 Hz, 4H, $CH_2CH_2NC(O)H$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 150.8, 129.1, 120.7, 116.9, 50.3, 49.2, 45.3, 39.8

Analytical data in accordance with literature.[324]

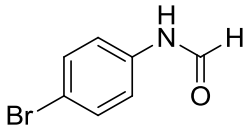
***N*-phenylformamide 47l**



General procedure F was followed. Eluent 20% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 90% yield (0.218 g, 1.80 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (br. s., 1H, N*H*) (minor), 8.62 (d, *J* = 11.3 Hz, 1H, (C=O)*H*) (minor), 8.25 (d, *J* = 1.7 Hz, 1H, (C=O)*H*) (major), 8.13 (br. s., 1H, N*H*) (major), 7.51 - 7.42 (m, 1H, Ar*H*), 7.30 - 7.17 (m, 2H, Ar*H*), 7.13 - 6.97 (m, 2H, Ar*H*). ^{13}C NMR (75MHz, $CDCl_3$) δ 163.0 (major), 159.5 (minor), 136.9 (minor), 136.7 (major), 129.6 (major), 129.0 (minor), 125.2 (major), 124.7 (minor), 120.0 (minor), 118.6 (major)

Analytical data in accordance with literature.[80]

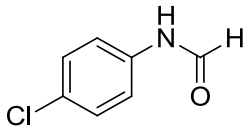
_N_-(4-bromophenyl)formamide 47m



General procedure F was followed. The reaction required the addition of 2 mL EtOAc and an extended reaction time of 24 h. The solvent was re-moved before purification. Eluent 15% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white crystalline solid in 95% yield (0.380 g, 1.90 mmol). m.p. 115-117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 11.3 Hz, 1H, (C=O)*H*) (minor), 8.40 (d, *J* = 1.5 Hz, 1H, (C=O)*H*) (major), 8.09 (br. s., 1H, N*H*) (minor), 7.52 - 7.47 (m, 2H, Ar*H*), 7.46 (s, 4H, Ar*H*) (major and minor), 7.32 (br. s., 1H, N*H*) (major), 7.02 - 6.95 (m, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (minor), 159.0 (major), 135.8 (major), 135.7 (minor), 132.7 (minor), 132.1 (major), 121.5 (major), 120.2 (minor), 118.2 (minor), 117.4 (major)

Analytical data in accordance with literature.[87]

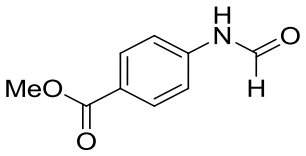
_N_-(4-chlorophenyl)formamide 47n



General procedure F was followed. The reaction required the addition of 2 mL EtOAc and an extended reaction time of 24 h. The solvent was re-moved before purification. Eluent 15% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a beige crystalline solid in 94% yield (0.292 g, 1.88 mmol). m.p. 101-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (br. s., 1H, N*H*) (minor), 8.52 - 8.44 (m, 1H, (C=O)*H*) (minor), 8.19 (d, *J* = 1.9 Hz, 1H, (C=O)*H*) (major), 7.38 - 7.29 (m, 2H, Ar*H*), 7.63 (br. s., 1H, N*H*) (major), 7.19 - 7.07 (m, 4H, Ar*H*), 6.93 - 6.82 (m, 2H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7 (minor), 159.2 (major), 135.4 (major), 135.2 (minor), 130.7, 129.8, 129.1, 121.2, 120.0

Analytical data in accordance with literature.[323]

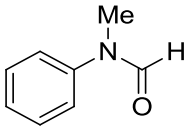
Methyl 4-formamidobenzoate 47o



General procedure F was followed. The reaction required the addition of 2 mL EtOAc and an extended re-action time of 24 h. The solvent was removed before purification. Eluent 15% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title com-pound as a white crystalline solid in 87% yield (0.311 g, 1.74 mmol). m.p. 123-125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, J = 11.1 Hz, 1 H, (C=O)*H*) (minor), 8.66 (d, J = 11.1 Hz, 1H, N*H*) (minor), 8.44 (d, J = 1.7 Hz, 1H, (C=O)H) (major), 8.09 - 7.97 (m, 4H, ArH), 7.80 (br. s., 1H, NH) (major), 7.69 - 7.59 (m, 2H, Ar*H*), 7.19 - 7.12 (m, 2H, Ar*H*), 3.92 (s, 3H, OCH_3) (minor), 3.91 (s, 3H, OCH_3) (major). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 166.3, 162.0, 159.1, 140.9, 131.5, 130.9, 126.5, 126.1, 119.1, 117.1, 52.2, 52.1.

Analytical data in accordance with literature.[325]

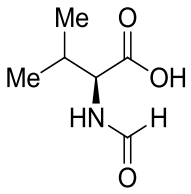
***N*-methyl-*N*-phenylformamide 47p**



General procedure F was followed. Eluent 10% EtOAc in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale brown oil in 91% yield (0.243 g, 1.82 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H, (C=O)*H*) (major), 8.17 (s, 1H, (C=O)*H*) (minor), 7.26 - 7.18 (m, 2H, Ar*H*), 7.13 - 7.04 (m, 1H, Ar*H*), 7.02 - 6.95 (m, 2H, Ar*H*), 3.16 (s, 3H, NCH_3) (minor), 3.13 (s, 3H, NCH_3) (major). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (major), 162.0 (minor), 141.9, 129.4 (major), 128.8 (minor), 126.1 (major), 126.0 (minor), 123.3 (minor), 122.0 (major), 36.6 (minor), 31.8 (major)

Analytical data in accordance with literature.[323]

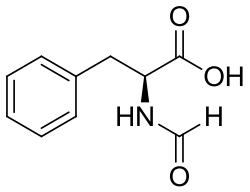
_N_-Formyl valine 49a



General procedure G was followed. Recrystallized to give the title compound as a white solid in 78% yield (0.113 g, 0.78 mmol). $[\alpha]_D^{20}$ = -11 in MeOH. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.8 (s, 1H, O*H*), 8.3 (d, *J* = 8.7 Hz, 1H, N*H*), 8.1 (s, 1H, (C=O)*H*), 4.2 (dd, *J* = 8.8, 5.3 Hz, 1H, C*H*NH), 2.1 (tq, *J* = 13.6, 6.8 Hz, 1H, C*H*$(CH_3)_2$), 0.9 (dd, *J* = 6.8, 4.7 Hz, 6H, CH(CH_3)$_2$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7, 161.2, 55.6, 29.9, 19.2, 17.7.

Analytical data in accordance with literature[80]

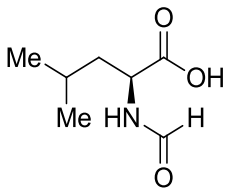
_N_-Formyl phenylalanine 49b



General procedure G was followed. Recrystallized to give the title compound as a cream solid in 86% yield (0.166 g, 0.86 mmol). $[\alpha]_D^{20}$ = +63 in MeOH. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.8 (s, 1H, O*H*), 8.4 (d, *J* = 8.0 Hz, 1H, N*H*), 8.0 (dd, *J* = 1.7, 0.8 Hz, 1H, (C=O)*H*), 7.3 – 7.2 (m, 2H, Ar*H*), 7.3 – 7.2 (m, 4H, Ar*H*), 4.5 (dddd, *J* = 9.1, 8.2, 5.0, 0.9 Hz, 1H, C*H*NH), 3.1 – 2.8 (m, 2H, CH_2Ph). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.5, 160.9, 137.3, 129.1, 128.2, 126.5, 51.9, 36.7.

Analytical data in accordance with literature.[80]

_N_-Formyl leucine 49c

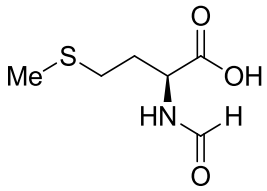


General procedure G was followed. Recrystallized to give the title compound as a white solid in a 74% yield (0.118 g, 0.74 mmol). $[\alpha]_D^{20}$ = -19 in MeOH. ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.1 (s, 1H, (C=O)*H*), 4.5 (dd, *J* = 9.2, 5.1 Hz, 1H, C*HNH*), 1.8 – 1.5 (m, 3H, C*H*$(CH_3)_2$ and CH_2CHNH),

1.0 (dd, *J* = 8.0, 6.1 Hz, 6H, CH(CH_3)$_2$). ^{13}C NMR (75 MHz, MeOD-d_4) δ 175.4, 163.6, 50.6, 41.9, 26.0, 23.3, 21.8.

Analytical data in accordance with literature.[80]

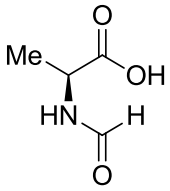
_N_-Formyl methionine 49d



General procedure G was followed. Recrystallized to give the title compound as a pale yellow solid in 81% yield (0.143 g, 0.81 mmol). $[\alpha]_D^{20}$ = +7.5 in MeOH. ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.1 (s, 1H, (C=O)*H*), 4.6 (dd, *J* = 8.7, 4.7 Hz, 1H, C*H*NH), 2.7 – 2.4 (m, 2H, CH_3SCH_2), 2.2 – 2.1 (m, 1H, $CH_3SCH_2CH_aH_b$), 2.1 (s, 3H, CH_3), 2.0 (dtd, *J* = 14.1, 8.4, 5.8 Hz, 1H, $CH_3SCH_2CH_aH_b$). ^{13}C NMR (75 MHz, MeOD-d_4) δ 174.4, 163.6, 51.3, 32.4, 31.0, 15.2.

Analytical data in accordance with literature.[80]

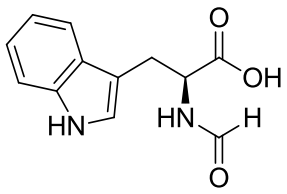
_N_-Formyl alanine 49e



General procedure G was followed. Recrystallized to give the title compound as a white solid in 89% yield (0.104 g, 0.89 mmol). $[\alpha]_D^{20}$ = -35.5 in MeOH. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 (s, 1H, (C=O)*H*), 4.5 (q, *J* = 7.3 Hz, 1H, C*H*CH_3), 1.4 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 163.3, 48.0, 18.0.

Analytical data in accordance with literature.[80]

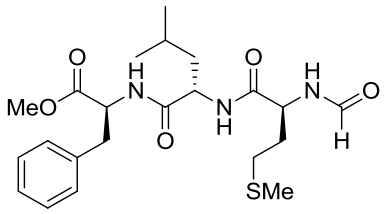
***N*-Formyl tryptophan 49f**



General procedure G was followed. Recrystallized to give the title compound as a pale brown solid in a 71% yield (0.165 g, 0.71 mmol). $[\alpha]_D^{20}$ = -36 in MeOH. ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.0 (s, 1H, (C=O)*H*), 7.6 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.3 (dd, *J* = 7.8, 1.2 Hz, 1H, Ar*H*), 7.1 – 7.0 (m, 2H, Ar*H*), 7.1 – 6.9 (m, 2H, Ar*H*), 4.8 (dd, *J* = 7.3, 5.1 Hz, 1H, C*H*NH), 3.4 – 3.3 (m, 1H, CH_aH$_b$Ar), 3.2 (dd, *J* = 14.7, 7.4 Hz, 1H, CH$_a$$H_b$Ar). ^{13}C NMR (75 MHz, MeOD-d_4) δ 174.6, 163.6, 138.0, 128.8, 124.4, 122.4, 119.8, 119.3, 112.2, 110.5, 53.2, 28.6.

Analytical data in accordance with literature.[80]

(*S*)-Methyl 2-((*S*)-2-((*S*)-2-formamido-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoate (Formyl-methionine-leucine-phenylalanine-OMe) 56.6

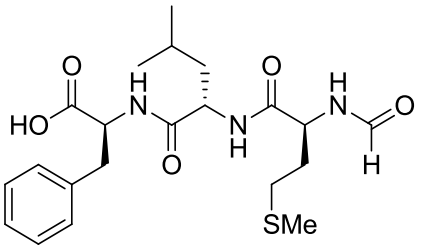


(6*S*,9*S*,12*S*)-methyl 12-benzyl-9-isobutyl-2,2-dimethyl-6-(2-(methylthio)ethyl)-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate[92] (0.80 g, 1.5 mmol) was dissolved in saturated methanolic HCl and stirred at rt for 1 h. The reaction was then concentrated *in vacuo*, the residue was suspended in EtOAc and neutralised with saturated $NaHCO_3$. The aqueous layers was further extracted with EtOAc (3x 30 mL), the organics were combined dried ($MgSO_4$) and concentrated *in vacuo* to give (*S*)-methyl 2-((*S*)-2-((*S*)-2-amino-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoate which was taken forward to the next step without further purification.

(formyloxy)(phenyl)methyl acetate (0.145 g, 0.75 mmol) was added to (*S*)-methyl 2-((*S*)-2-((*S*)-2-amino-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoate (0.213 g, 0.50 mmol) in EtOAc (4 mL) the reaction was stirred at rt for 5 h. The crude reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$, the organics were then dried

($MgSO_4$) and concentrated *in vacuo*. The residue was purified *via* recrystallization (MeOH/H_2O) to give the title compound in 87% yield (0.20 g, 0.44 mmol); m.p. 133-135 °C, $[\alpha]_D^{20}$ = -38 in MeOH. ^{1}H NMR (300 MHz, MeOD-d4) δ 8.09 (s, 1H, (C=O)*H*), 7.34 - 7.15 (m, 5H, Ar*H*), 4.64 (dd, *J* = 5.8, 8.5 Hz, 1H, $PhCH_2CH$), 4.51 (dd, *J* = 5.5, 8.1 Hz, 1H, $MeSCH_2CH_2CH$), 4.41 (dd, *J* = 7.0, 8.1 Hz, 1H, $CH(CH_3)_2CH_2CH$), 3.68 (s, 3H, OCH_3), 3.15 (dd, *J* = 5.8, 13.8 Hz, 1H, $PhCH_aH_bCH$), 3.00 (dd, *J* = 8.7, 13.9 Hz, 1H, $PhCH_aH_bCH$), 2.56 - 2.38 (m, 2H, $MeSCH_2CH_2CH$), 2.07 (s, 3H, SCH_3), 2.03 - 1.80 (m, 2H, $MeSCH_2CH_2CH$), 1.72 - 1.59 (m, 1H, $CH(CH_3)_2CH_2CH$), 1.52 (t, *J* = 7.0 Hz, 2H, $CH(CH_3)_2CH_2CH$), 0.92 (dd, *J* = 12.8, 6.4 Hz, 6H, $CH(CH_3)_2CH_2CH$). ^{13}C NMR (75 MHz, MeOD-d_4) δ 174.4, 173.2, 173.0, 163.7, 138.0, 130.3, 129.5, 127.9, 116.0, 55.2, 52.9, 52.7, 52.4, 41.9, 38.3, 33.0, 30.8, 25.8, 23.4, 22.0, 15.2. I.R (thinfilm) *v* max (cm^{-1}): 3279 ((C=O)NH), 1738, 1664, 1632 (C=O); HRMS (ESI): m/z calculated for $C_{22}H_{33}N_3O_5S$: requires: 452.2219 for $[M+H]^+$; found: 452.2245.

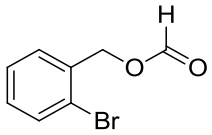
(S)-2-((S)-2-((S)-2-formamido-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoic acid (Formyl-methionine-leucine-phenylalanine-OH) 56.7



2 M $NaOH_{(aq)}$ (1 mL) was added to a stirred solution of (*S*)-Methyl 2-((*S*)-2-((*S*)-2-formamido-4-(methylthio)butanamido)-4-methylpentanamido)-3-phenylpropanoate (0.20 g, 0.44 mmol) dissolved in MeOH (5mL). The reaction was stirred at rt for 2 h. The MeOH was removed under reduced pressure and the reaction was diluted with H_2O, the aqueous solution was then extracted with Et_2O (3x 15 mL). The aqueous layers was then acidified with 1 M $HCl_{(aq)}$ and extracted with EtOAc (3x 20 mL). The second organics were then dried ($MgSO_4$) and concentrated *in vacuo,* the residue was then purified *via* recrystallization (MeOH/H_2O) to give the title compound in 93% yield (0.179 g, 0.40 mmol); m.p. 208-210 °C, $[\alpha]_D^{20}$ = -18 in MeOH/ -9 in AcOH. ^{1}H NMR (300 MHz, MeOD-d4) δ 8.08 (s, 1 H, (C=O)*H*), 7.33 - 7.14 (m, 5H, Ar*H*), 4.69 - 4.59 (m, 1H, $PhCH_2CH$), 4.51 (dd, *J* = 5.7, 7.9 Hz, 1H, $MeSCH_2CH_2CH$), 4.42 (t, *J* = 7.7 Hz, 1H, $CH(CH_3)_2CH_2CH$), 3.27 - 3.13 (m, 1H, $PhCH_aH_bCH$), 3.08 - 2.91 (m, 1H, $PhCH_aH_bCH$), 2.55 - 2.39 (m, 2H, $MeSCH_2CH_2CH$), 2.06 (s, 3H, SCH_3), 2.02 - 1.78 (m, 2H, $MeSCH_2CH_2CH$), 1.65 (dt, *J* = 6.6, 13.5 Hz, 1H, $CH(CH_3)_2CH_2CH$), 1.58 - 1.47 (m, 2H, $CH(CH_3)_2CH_2CH$), 0.96 - 0.85 (m, 6H, $CH(CH_3)_2CH_2CH$). ^{13}C NMR (75MHz, MeOD-d4) δ 174.5, 173.2, 163.8, 138.4, 130.5, 129.6, 128.0, 55.1, 53.1, 52.5,

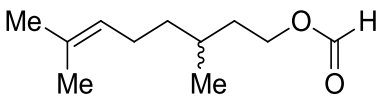
42.1, 38.4, 33.1, 31.0, 25.9, 23.5, 22.1, 15.4. I.R (thinfilm) *v* max (cm^{-1}): 3284 ((C=O)NH), 1729, 1634, 1621 (C=O); HRMS (ESI): m/z calculated for $C_{21}H_{31}N_3O_5S$: requires: 438.2062 for $[M+H]^+$; found: 438.2080.

2-Bromobenzyl alcohol formate 52a



General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 80% yield (0.172 g, 0.80 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H, (C=O)*H*), 7.61 (dd, *J* = 1.2, 8.1 Hz, 1H, Ar*H*), 7.45 (dd, *J* = 2.0, 7.8 Hz, 1H, Ar*H*), 7.34 (dt, *J* = 1.2, 7.5 Hz, 1H, Ar*H*), 7.25 - 7.20 (m, 1H, Ar*H*), 5.31 (s, 2H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 134.5, 132.9, 130.1, 130.0, 127.6, 123.5, 65.2. I.R (thinfilm) *v* max (cm^{-1}): 1719 (C=O); HRMS (ESI): m/z calculated for $C_8H_7BrO_2$: requires: 214.9629 for $[M+H]^+$; found: 214.9974.

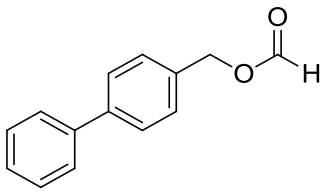
Citronellyl formate 52b



General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 83% yield (0.153 g, 0.83 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H, (C=O)*H*), 5.19 - 4.98 (m, 1H, C=C*H*), 4.29 - 4.11 (m, 2H, CH_2O(C=O)H), 2.12 - 1.83 (m, 2H,), 1.81 - 1.64 (m, 4H), 1.61 (s, 3H, C=CCH_3), 1.58 - 1.29 (m, 3H), 1.27 - 1.14 (m, 1H), 0.93 (d, *J* = 6.4 Hz, 3H, CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 131.4, 124.5, 62.5, 36.9, 35.3, 29.4, 25.7, 25.4, 19.3, 17.6.

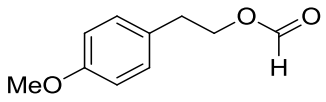
Analytical data in accordance with literature.[326]

Biphenyl-4-methanol formate 52c



General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as crystalline white solid in 80% yield (0.170 g, 0.80 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.18 (t, *J* = 0.9 Hz, 1H, (C=O)*H*), 7.65 - 7.57 (m, 4H, Ar*H*), 7.50 - 7.42 (m, 4H, Ar*H*), 7.41 - 7.34 (m, 1H, Ar*H*), 5.27 (s, 2H, C*H*$_2$O(C=O)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 141.5, 140.5, 134.1, 128.9, 128.8, 127.5, 127.4, 127.1, 65.5. I.R (thinfilm) *v* max (cm^{-1}): 1702 (C=O); HRMS (ESI): m/z calculated for $C_{14}H_{12}O_2$: requires: 213.0915 for $[M+H]^+$; found: 213.1055.

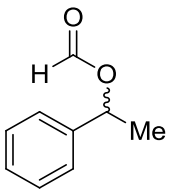
4-Methoxy phenethyl alcohol formate 52d



General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 71% yield (0.127 g, 0.71 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H, (C=O)*H*), 7.19 - 7.10 (m, 2H, Ar*H*), 6.91 - 6.81 (m, 2H, Ar*H*), 4.36 (t, *J* = 7.0 Hz, 2H, C*H*$_2$(OC=O)), 3.81 (s, 3H, C*H*$_3$), 2.93 (t, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_2$(OC=O)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 158.4, 129.8, 129.3, 113.9, 64.6, 55.2, 34.0.

Analytical data in accordance with literature.[326]

1-Phenylethanol formate 52e

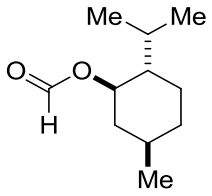


General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 75% yield (0.112 g, 0.75 mmol). ^{1}H NMR (300 MHz,

$CDCl_3$) δ 8.11 (s, 1 H, (C=O)*H*), 7.42 - 7.28 (m, 5H, ArH), 6.18 - 5.85 (m, 1H, C*H*(OC=O)), 1.60 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75MHz, $CDCl_3$) δ 160.4, 140.8, 128.6, 128.1, 126.1, 72.2, 22.1.

Analytical data in accordance with literature.[326]

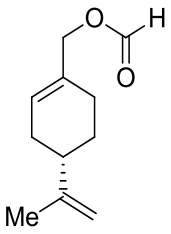
Menthol formate 52f



General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 78% yield (0.143 g, 0.78 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 0.8 Hz, 1H, (C=O)*H*), 4.81 (dt, *J* = 4.3, 10.8 Hz, 1H, C*H*(OC=O)), 2.07 - 1.97 (m, 1H, C*H*), 1.91 (dtd, *J* = 2.6, 7.0, 13.9 Hz, 1H, C*H*), 1.76 - 1.64 (m, 2H, CH_2), 1.59 - 1.33 (m, 2H, CH_2), 1.14 - 0.98 (m, 2H, CH), 0.95 - 0.84 (m, 7H, C*H* & CH(CH_3)$_2$), 0.77 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 74.1, 46.8, 40.8, 34.1, 31.4, 26.0, 23.2, 22.0, 20.7, 16.0.

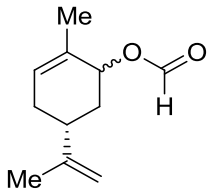
Analytical data in accordance with literature.[327]

Perillyl alcohol formate 52g



General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in 88% yield (0.159 g, 0.88 mmol). $[\alpha]_D^{20}$ = -62.5 in MeOH. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H, (C=O)*H*), 5.86 - 5.76 (m, 1H, CH_2C=C*H*), 4.77 - 4.70 (m, 2H, C=CH_2), 4.57 (s, 2H, CH_2O(C=O)), 2.26 - 2.06 (m, 4H, CH_2), 2.05 - 1.94 (m, 1H, C*H*), 1.93 - 1.80 (m, 1H, C*H*), 1.75 (s, 3H, CH_3), 1.60 - 1.41 (m, 1H, C*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 149.4, 132.0, 126.8, 108.8, 68.0, 40.7, 30.4, 27.2, 26.3, 20.7. I.R (thinfilm) *v* max (cm^{-1}): 1722 (C=O); HRMS (ESI): m/z calculated for $C_{11}H_{16}O_2$: requires: 181.1228 for $[M+H]^+$; found: 181.1210.

Carveol formate 52h

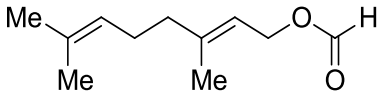


General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil in a 84% yield (0.150 g, 0.84 mmol)

Product obtained as a mixture of diastereomers (1:1) in the same ratio as the starting material.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 1.1 Hz, 1H, (C=O)*H*), 8.14 (s, 1H, (C=O)*H*), 5.82 - 5.75 (m, 1H), 5.68 - 5.53 (m, 2H), 5.44 - 5.37 (m, 1H), 4.78 - 4.74 (m, 2H), 4.74 - 4.70 (m, 2H), 2.40 - 2.06 (m, 5H), 2.04 - 1.82 (m, 4H), 1.76 - 1.68 (m, 10H), 1.68 - 1.63 (m, 3H), 1.61 - 1.56 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1 (α), 161.0 (β), 148.5 (α), 148.1(β), 132.1 (α), 130.2(β), 128.6 (α), 126.5(β), 109.5 (α), 109.4(β), 73.1 (α), 70.5(β), 40.2 (α), 35.7(β), 33.9 (α), 33.7(β), 30.8 (α), 30.7(β), 20.8 (α), 20.5(β), 20.5 (α), 18.8 (β). I.R (thinfilm) *v* max (cm^{-1}): 1717 (C=O); HRMS (ESI): m/z calculated for $C_{11}H_{16}O_2$: requires: 181.1228for $[M+H]^+$; found: 181.1190.

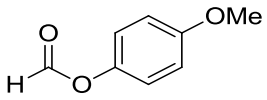
Geranyl formate 52i



General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil in 85% yield (0.155 g, 0.85 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H, (C=O)*H*), 5.45 - 5.31 (m, 1H C=C*H*CH_2O), 5.20 - 5.00 (m, 1H, C=C*H*CH_2), 4.70 (d, *J* = 7.2 Hz, 2H, C*H*$_2$O(C=O)), 2.17-2.06 (m, 4H, C*H*$_2$C*H*$_2$), 1.76 - 1.71 (m, 3H C*H*$_3$C(CH_3)=CH), 1.71 - 1.67 (m, 3H, CH_3C(C*H*$_3$)=CH), 1.61 (s, 3H, CH_2C(C*H*$_3$)=CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 143.2, 131.9, 123.6, 117.6, 60.8, 39.5, 26.2, 25.7, 17.7, 16.5.

Analytical data in accordance with literature.[328]

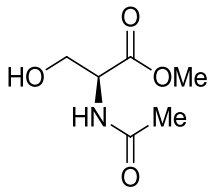
4-Methoxyphenol formate 52j



General procedure H was followed. Eluent 5% EtOAc in pet ether the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as an orange oil in a 75% yield (0.114 g, 0.75 mmol). ^{1}H NMR (300MHz, $CDCl_3$) δ 8.30 (s, 1H, (C=O)*H*), 7.12 - 7.01 (m, 2H, Ar*H*), 6.96 - 6.87 (m, 2H, Ar*H*), 3.82 (s, 3H, CH_3). ^{13}C NMR (75MHz, $CDCl_3$) δ 159.7, 157.6, 143.3, 122.0, 114.6, 55.

Analytical data in accordance with literature.[329]

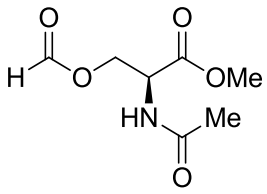
(*S*)-methyl 2-acetamido-3-hydroxypropanoate 53.2



Serine methyl ester hydrochloride salt (0.5 g, 3.21 mmol) was suspended in acetone (3 mL), to this was added NEt_3 (0.42 mL, 3.21 mmol) dropwise. The mixture was stirred for 10 min and then filtered through a Celite® pad. The filtrate was concentrated *in vacuo* to give serine methyl ester which was used without further purification.

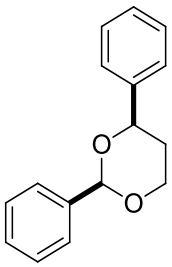
General procedure A was followed. Eluent 5% MeOH in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a brown oil in 83% yield (0.428 g, 2.56 mmol), $[\alpha]_D^{20}$ = -9.5 MeOH; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.5 (s, 1H, N*H*), 4.7 (dt, *J* = 7.3, 3.6 Hz, 1H, C*H*NH), 4.0 – 3.9 (m, 2H, CH_2OH), 3.8 (s, 3H, OCH_3), 2.8 (s, 1H, O*H*), 2.1 (s, 3H, (C=O)CH_3), ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 170.8, 63.6, 54.9, 52.9, 23.3. $[\alpha]_D^{20}$ = -9.5 in MeOH. I.R (thinfilm) *v* max (cm^{-1}): 3291 ((C=O)NH and OH), 1738, 1648 (C=O); HRMS (ESI): m/z calculated for $C_6H_{11}NO_4$: requires: 162.0766 for $[M+H]^+$; found: 162.0788.

(*S*)-methyl 2-acetamido-3-(formyloxy)propanoate 53.3



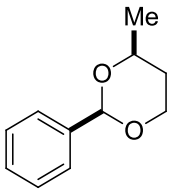
General procedure H was followed. Eluent 5% MeOH in CH_2Cl_2 the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a white solid in 78% yield (0.377 g, 2.0 mmol); m.p. 95-97 °C, $[\alpha]_D^{20}$ = -56 $CHCl_3$. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.0 (q, *J* = 0.9 Hz, 1H, (C=O)*H*), 6.3 (s, 1H, N*H*), 4.9 (dt, *J* = 7.1, 3.3 Hz, 1H, C*H*NH), 4.6 – 4.4 (m, 2H, C*H*$_2$O(C=O)H), 3.8 (s, 3H, OC*H*$_3$), 2.1 (s, 3H, (C=O)C*H*$_3$). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 170.0, 169.9, 160.3, 63.6, 53.2, 51.6, 23.2. I.R (thinfilm) *v* max (cm^{-1}): 3292 ((C=O)NH), 1727, 1713, 1703 (C=O); HRMS (ESI): m/z calculated for $C_7H_{11}NO_5$: requires: 190.0715 for $[M+H]^+$; found: 190.0739.

2,4-diphenyl-1,3-dioxane 54.2



General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 85% yield. (0.204 g, 0.85 mmol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H, Ar*H*), 7.5 – 7.3 (m, 8H, Ar*H*), 5.7 (s, 1H, OC*H*O), 4.9 (dd, *J* = 11.4, 2.6 Hz, 1H, OC*H*CH$_a$H$_b$), 4.4 (ddd, *J* = 11.5, 5.0, 1.4 Hz, 1H, OC*H*$_a$H$_b$), 4.2 (td, *J* = 11.9, 2.5 Hz, 1H, OCH$_a$*H*$_b$), 2.3 – 2.0 (m, 1H, OCHC*H*$_a$H$_b$), 1.8 (dtd, *J* = 13.5, 2.5, 1.4 Hz, 1H, OCHCH$_a$*H*$_b$), ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 138.8, 129.0, 128.6, 128.4, 127.9, 126.3, 126.0, 101.7, 79.2, 67.5, 33.6. I.R (thinfilm) *v* max (cm^{-1}): 2962, 2853 (Ar C-H); HRMS (ESI): m/z calculated for $C_{16}H_{16}O_2$: requires: 263.1048 for $[M+H]^+$; found: 263.1030.

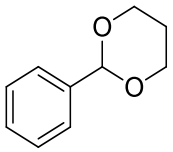
4-methyl-2-phenyl-1,3-dioxane 57a



General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 80% yield. (0.142 g, 0.80 mmol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 – 7.4 (m, 2H, Ar*H*), 7.4 – 7.3 (m, 3H, Ar*H*), 5.5 (s, 1H, OC*H*O), 4.3 (ddd, *J* = 11.4, 5.0, 1.4 Hz, 1H, C*H*CH_3), 4.1 – 3.8 (m, 2H, OC*H*$_2$$CH_aH_b$), 1.8 (dddd, *J* = 13.4, 12.4, 11.0, 5.0 Hz, 1H, $OCH_2CH_aH_b$), 1.5 (dtd, *J* = 13.3, 2.5, 1.4 Hz, 1H, $OCH_2CH_aH_b$), 1.3 (d, *J* = 6.2 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 128.9, 128.4, 126.2, 101.5, 73.6, 67.2, 33.1, 22.0.

Analytical data in accordance with literature.[330]

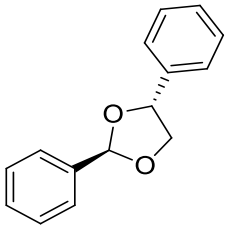
2-phenyl-1,3-dioxane 57b



General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 80% yield. (0.131 g, 0.80 mmol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 – 7.4 (m, 2H, ArH), 7.4 – 7.3 (m, 3H, ArH), 5.5 (s, 1H, OC*H*O), 4.3 (ddt, *J* = 10.5, 5.0, 1.4 Hz, 2H, 2 x OC*H*$_a$$H_b$), 4.1 – 3.9 (m, 2H, 2 x OCH_aH_b), 2.2 (dtt, *J* = 13.5, 12.4, 5.0 Hz, 1H, $CH_2H_aH_bCH_2$), 1.5 (dtt, *J* = 13.5, 2.7, 1.4 Hz, 1H, $CH_2H_aH_bCH_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 128.9, 128.4, 126.1, 101.8, 67.5, 25.9.

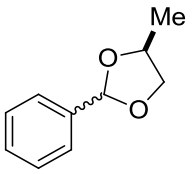
Analytical data in accordance with literature.[331]

(2R,4R)-2,4-diphenyl-1,3-dioxolane 57c



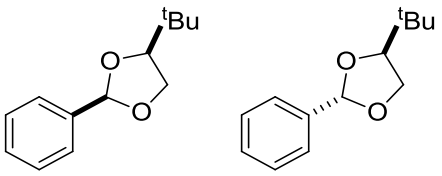
General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 88% yield. (0.199 g, 0.88 mmol), $[\alpha]_D^{20}$ = -100 in $CHCl_3$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 – 7.5 (m, 2H, Ar*H*), 7.5 – 7.3 (m, 8H, Ar*H*), 6.2 (s, 1H, OC*H*O), 5.2 (dd, *J* = 7.7, 6.4 Hz, 1H, OC*H*CH_aH_b), 4.5 (dd, *J* = 8.3, 6.3 Hz, 1H, OCHC*H*$_a$$H_b$), 4.0 – 3.8 (m, 1H, OCHCH_a*H*$_b$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 138.3, 129.4, 128.8, 128.6, 128.3, 126.5, 126.2, 104.7, 78.0, 72.9., I.R (thinfilm) *v* max (cm^{-1}): 2965, 2848 (Ar C-H); HRMS (ESI): m/z calculated for $C_{15}H_{14}O_2$: requires: 227.1072 for $[M+H]^+$; found: 227.1068.

4-methyl-2-phenyl-1,3-dioxolane 57d



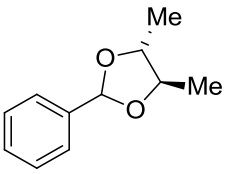
General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 82% yield as a mix of diastereomers (2:3 syn:anti). (0.134 g, 0.82 mmol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 – 7.4 (m, 4H, ArH, **syn** and **anti**), 7.4 – 7.3 (m, 6H, ArH, **syn** and **anti**), 6.0 (s, 1H, OC*H*O, **syn**), 5.8 (s, 1H, OC*H*O, **anti**), 4.4 – 4.3 (m, 2H, C*H*CH_3, **syn** and **anti**), 4.3 (dd, *J* = 7.8, 6.0 Hz, 1H, CHC$H_a$$H_b$, **syn**), 4.1 (dd, *J* = 7.5, 6.5 Hz, 1H, CHC$H_a$$H_b$, **anti**), 3.7 – 3.5 (m, 2H, $CHCH_aH_b$, **syn** and **anti**), 1.4 (d, *J* = 6.1 Hz, 3H, CHCH_3, **anti**), 1.4 (d, *J* = 6.1 Hz, 3H, CHCH_3, **syn**). ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.4, 129.2, 128.5, 126.7, 126.5, 104.2, 103.2, 73.6, 72.5, 72.2, 71.6, 18.7, 18.5, mix of **syn** and **anti**. I.R (thinfilm) *v* max (cm^{-1}): 2961, 2868 (Ar C-H); HRMS (ESI): m/z calculated for $C_{10}H_{12}O_2$: requires: 187.0735 for $[M+Na]^+$; found: 187.0376.

4-(tert-butyl)-2-phenyl-1,3-dioxolane 57e



General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 78% yield, as a mixture of separateable diastereomers (0.161 g, 0.78 mmol); **Syn:** ^{1}H NMR (300 MHz, $CDCl_3$)) δ 7.5 – 7.4 (m, 2H, ArH), 7.4 – 7.3 (m, 3H, ArH), 5.9 (s, 1H, OC*H*O), 4.1 (dd, *J* = 8.0, 6.3 Hz, 1H, C*H*C(CH)$_3$), 3.9 (dd, *J* = 8.1, 6.3 Hz, 1H, CH_aH_b), 3.8 (t, *J* = 8.1 Hz, 1H, CH_aH_b), 1.0 (s, 9H, CHC(C*H*)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$)) δ 138.9, 129.1, 128.5, 126.5, 104.4, 84.2, 66.8, 33.5, 25.7. **Anti:** ^{1}H NMR (300 MHz, $CDCl_3$)) δ 7.6 – 7.5 (m, 2H, ArH), 7.4 – 7.3 (m, 3H, ArH), 5.8 (s, 1H, OC*H*O), 4.0 – 3.9 (m, 3H, C*H*CH_2), 1.0 (s, 9H, CHC(C*H*)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$)) δ 137.6, 129.5, 128.5, 127.0, 104.1, 84.8, 66.4, 33.1, 25.7. I.R (thinfilm) *v* max (cm^{-1}): 2956, 2871 (Ar C-H); HRMS (ESI): m/z calculated for $C_{13}H_{18}O_2$: requires: 205.1228 for [M-H]$^-$; found: 205.1229.

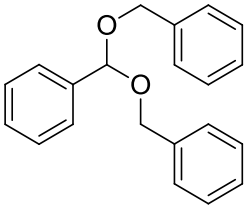
(4R,5R)-4,5-dimethyl-2-phenyl-1,3-dioxolane 57f



General procedure I was followed. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 84% yield. (0.150 g, 0.84 mmol), $[\alpha]_D^{20}$ = -33 in $CHCl_3$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 – 7.5 (m, 2H, ArH), 7.4 – 7.3 (m, 3H, ArH), 5.9 (s, 1H, OC*H*O), 3.8 (dtt, *J* = 7.4, 5.3, 2.7 Hz, 2H, 2 x C*H*CH$_3$), 1.4 – 1.4 (m, 3H, CHC*H*$_3$), 1.4 – 1.3 (m, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$)) δ 138.7, 129.3, 128.5, 126.6, 102.8, 80.5, 78.8, 17.4, 17.1.

Analytical data in accordance with literature.[332, 333]

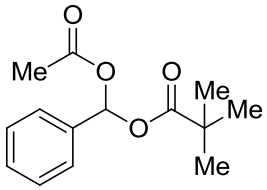
(((phenylmethylene)bis(oxy))bis(methylene))dibenzene 57g



Benzyl alcohol (0.216 g, 2.0 mmol) and acetic acid (0.65 µL, 0.01 mmol) were added to phenylmethylene diacetate (0.208 g, 1.0 mmol) in MeCN (3 mL) and heated to 40 °C for 12 h. The crude reaction mixture was concentrated under vacuum and the resulting residue was purified by column chromatography to give the isolated acetal. Eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil in 66% yield (0.200 g, 0.66 mmol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.6 – 7.2 (m, 15H, ArH), 5.8 (d, J = 3.6 Hz, 1H, OC*H*O), 4.6 (s, 4H, CH_2Ph). ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.5, 138.1, 128.6, 128.3, 128.3, 127.6, 127.5, 126.6, 100.6, 67.1.

Analytical data in accordance with literature.[334]

Acetoxy(phenyl)methyl pivalate 58.3



General procedure C was followed. Further purified by column chromatography, eluent 5% EtOAc in pet ether, the fractions containing product were combined and the solvent was evaporated under reduced pressure to give the title compound as a clear oil a 60% yield (1.41 g, 5.64 mmol). ^{1}H NMR (300 MHz, $CDCl_3$)) δ 7.7 (s, 1H, OC*H*O), 7.6 – 7.4 (m, 2H, Ar*H*), 7.5 – 7.3 (m, 3H, Ar*H*), 2.1 (s, 3H, C(O)CH_3), 1.2 (s, 9H, C(O)C(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$)) δ 176.4, 169.1, 135.8, 129.7, 128.7, 126.7, 89.9, 39.0, 27.0, 21.1.

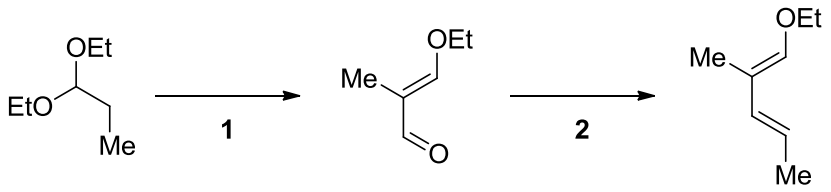
Protecting Group Free Synthesis towards Polyketide Natural Products

Enantiomeric excess analysis

Enantiomeric excess was determined by gas chromatography (GC), model Agilent 7890A fitted with three detectors. A flame ionisation detector (FID), a thermal conductivity detector (TCD) and an Agilent 5975C Mass Spec. The column used for analysis was a β-Dex 30 m long

0.530 mm in diameter. Method initial temperature: 80 °C held for 2 min, heated to 230 °C at a ramp of 10 °C min^{-1} and held at that final temperature for 2 min.

Synthesis of (*1E,3E*)-1-ethoxy-2-methylpenta-1,3-diene 96.1 Route one



Step 1: (*E*)-3-ethoxy-2-methylacrylaldehyde 94.2

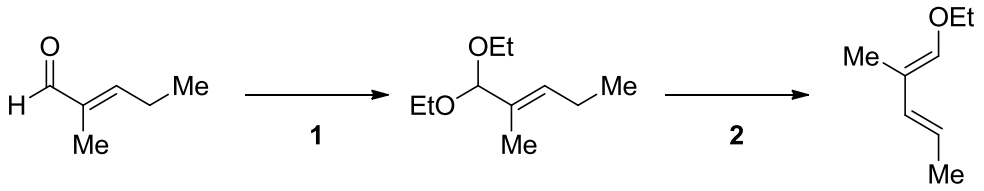
N,N-Dimethylformamide (14 mL, 182.4 mmol) was added dropwise to phosphorus(V) oxychloride (15.6 mL, 167.2 mmol) at 0 °C with vigorous stirring. Propionaldehyde diethyl acetal **94.1** (10 g, 12.3 mL, 76 mmol) was then slowly added to the reaction mixture ensuring that reaction temperature does not exceed 40 °C. Upon completion of addition the reaction was heated to 70 °C for 2 h, the reaction was then poured over ice (30 g) and left overnight. The solution was then basified with K_2CO_3 and extracted with Et_2O (3x 100 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a pale yellow oil (2.6 g, 30%, 54.7 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H, C(O)*H*), 6.97 (d, *J* = 1.1 Hz, 1H, C*H*OEt), 4.18 (q, *J* = 7.2 Hz, 2H, C*H*$_3$CH$_3$), 1.69 (d, *J* = 1.1 Hz, 3H, C*H*$_3$), 1.40 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, CDCl3) δ 192.0, 167.9, 120.0, 71.0, 15.3, 6.4. I.R (thin film) ν max (cm^{-1}): 2983 (C=C-H), 1631 (C=O). HRMS (ESI): m/z calculated. $C_6H_{10}O_2$: requires 115.075905 for $[M+H]^+$; found: 115.0776; requires: 137.057849 for $[M+Na]^+$; found: 137.0590.

Step 2: (*1E,3E*)-1-ethoxy-2-methylpenta-1,3-diene 96.1

nBuLi (14.7 mL, 1.4 M in hexanes) was added slowly to a stirred solution of diisopropylamine (4.16 mL, 28.8 mmol) in THF (50 mL) at -78 °C and stirred for 10 min. The reaction was then warmed to 0 °C followed by the addition of ethyltriphenylphosphonium bromide (9.18 g, 25 mmol) the reaction was then allowed to warm to rt and stirred for 1 h. (*E*)-3-ethoxy-2-methylacrylaldehyde **20.2** (2.35 g, 20.6 mmol) was added dropwise and stirred for 2 h. The reaction was then diluted with H_2O (100 mL) and extracted with Et_2O (3x 50 mL), the combined organic layers were dried ($MgSO_4$) and carefully concentrated *in vacuo* to give a crude mixture of product and triphenylphosphine oxide. The product was purified by kugelrohr distillation under reduced pressure to give the title compound as a yellow oil (2.08 g, 80%, 16.5 mmol, B.P 75 °C at 40 milibar). (*1E, 3E*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 - 6.07 (m, 1 H, C*H*OEt), 5.96 (dd, *J* = 1.4, 15.4 Hz, 1 H, C*H*CHCH$_3$), 5.45 (qd, J = 6.6, 15.1 Hz, 1 H, CHC*H*CH$_3$), 3.83 (q, *J* =

7.2 Hz, 2 H, CH_2CH$_3$), 1.76 (dd, *J* = 1.3, 6.6 Hz, 3 H, CHCHCH_3), 1.71 (d, *J* = 1.1 Hz, 3 H, EtOCHCH_3), 1.27 (t, *J* = 7.1 Hz, 3 H, OCH$_2$CH_3). (*1E, 3Z*): ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.15 - 6.07 (m, 1 H, C*H*OEt), 5.70 (app d, *J* = 11.3 Hz, 1 H, C*H*CHCH$_3$), 5.31 (qd, *J* = 7.2, 11.7 Hz, 1 H, CHC*H*CH$_3$), 3.83 (q, *J* = 7.0 Hz, 2 H, CH_2CH$_3$), 1.76 (dd, *J* = 1.3, 6.6 Hz, 3 H, CHCHCH_3), 1.69 (d, *J* = 1.1 Hz, 3 H, EtOCHCH_3), 1.28 (t, *J* = 7.1 Hz, 3 H, OCH$_2$CH_3). ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.4, 130.8, 119.5, 114.3, 67.9, 18.3, 15.3, 9.6. I.R (thinfilm) ν max (cm^{-1}): 2978 (C=C-H), 2932 (C=C-H), 1650 (C=C), 1634 (C=C)

Synthesis of (*1E,3E*)-1-ethoxy-2-methylpenta-1,3-diene 96.1 Route two



Step 1: (*E*)-1,1-diethoxy-2-methylpent-2-ene 98.2

(*E*)-2-methylpentenal **98.1** (2 g, 2.4 mL, 20.36 mmol) was added to a stirred solution of triethylorthoformate (4.1 mL, 24.4 mmol) and ammonium nitrate (0.16 g, 2.04 mmol) in EtOH (15 mL) and stirred at rt for 18 h. The reaction was concentrated *in vacuo* the residues was then dissolved in Et$_2$O (50 mL) and washed with H$_2$O (3x 20 mL). The organic layer was then dried (MgSO$_4$) and concentrated *in vacuo* to give the title compound as a yellow oil (3.33 g, 95%, 19.34 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.52 (app t, *J* = 7.0 Hz, 1 H, C*H*CH$_2$CH$_3$), 4.58 (s, 1 H, (EtO)$_2$C*H*), 3.63 - 3.53 (m, 2 H, OCH_2CH$_3$), 3.50 - 3.39 (m, 2 H, OCH_2CH$_3$), 2.07 (ap quin, *J* = 7.4 Hz, 2 H, CHCH_2CH$_3$), 1.62 (s, 3 H, CH$_3$), 1.29 - 1.17 (m, 6 H, 2 X OCH$_2$CH_3), 0.98 (t, *J* = 7.5 Hz, 3 H, CHCH$_2$CH_3). ^{13}C NMR (75 MHz, CDCl$_3$) δ 132.0, 130.8, 106.1, 61.7, 20.6, 15.1, 13.9, 10.9. I.R (thin film) $_\nu$max (cm^{-1}): 2974 (C=C-H), 1693 (C=C). HRMS (ESI): m/z calculated. C$_{10}$H$_{20}$O$_2$: requires 195.135551 for [M+Na]$^+$; found: 195.1206.

Step 2: (*1E,3E*)-1-ethoxy-2-methylpenta-1,3-diene 96.1

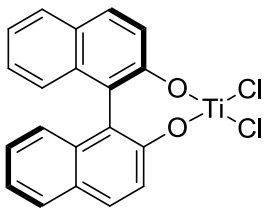
nBuLi (11.7 mL, 1.5M in hexanes) was added dropwise to a mixture of KO^{t}Bu (2 g, 17.6 mmol) in THF (20 mL) at -78 °C under a N$_2$ environment. (*E*)-1,1-diethoxy-2-methylpent-2-ene **98.2** (1.5 g, 1.7 mL, 8.8 mmol) was added dropwise to the reaction mixture to give a red mixture. The reaction was allowed to warm to rt and stirred for 24 h. The reaction was quenched with H$_2$O (15 mL) and extracted with Et$_2$O (3x 20 mL), the combined organic layers were dried (MgSO$_4$) and carefully concentrated *in vacuo* to give crude product. The residue was purified by short path distillation under reduced pressure to give the title compound as a yellow oil (0.66 g, 60%, 5.28 mmol, B.P 75 °C at 40 milibar). (*1E, 3E*): ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.15 - 6.07 (m, 1 H,

C*H*OEt), 5.96 (dd, *J* = 1.4, 15.4 Hz, 1 H, C*H*CHCH$_3$), 5.45 (qd, J = 6.6, 15.1 Hz, 1 H, CHC*H*CH$_3$), 3.83 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 1.76 (dd, *J* = 1.3, 6.6 Hz, 3 H, CHCHC*H*$_3$), 1.71 (d, *J* = 1.1 Hz, 3 H, EtOCHC*H*$_3$), 1.27 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$). (*1E, 3Z*): ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.15 - 6.07 (m, 1 H, C*H*OEt), 5.70 (app d, *J* = 11.3 Hz, 1 H, C*H*CHCH$_3$), 5.31 (qd, *J* = 7.2, 11.7 Hz, 1 H, CHC*H*CH$_3$), 3.83 (q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 1.76 (dd, *J* = 1.3, 6.6 Hz, 3 H, CHCHC*H*$_3$), 1.69 (d, *J* = 1.1 Hz, 3 H, EtOCHC*H*$_3$), 1.28 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.4, 130.8, 119.5, 114.3, 67.9, 18.3, 15.3, 9.6. I.R (thinfilm) $_v$max (cm^{-1}): 2978 (C=C-H), 2932 (C=C-H), 1650 (C=C), 1634 (C=C)

Step 2: (*1E,3E*)-1-ethoxy-2-methylpenta-1,3-diene 96.1

KO^{t}Bu (4.94 g, 44 mmol) was added to a solution of (*E*)-1,1-diethoxy-2-methylpent-2-ene **98.2** (3 g, 3.4 mL, 17.6 mmol) in DMSO (15 mL). The stirred solution was heated at 80 °C under a N_2 environment for 4 h. The reaction was quenched with H_2O (15 mL) and extracted with Et_2O (3x 20 mL), the combined organic layers were dried ($MgSO_4$) and carefully concentrated *in vacuo* to give a crude product. The residue was purified by short path distillation under reduced pressure to give the title compound as a clear oil (1.77 g, 80%, 14.08 mmol, B.P 75 °C at 40 milibar). (*1E, 3E*): ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.15 - 6.07 (m, 1 H, C*H*OEt), 5.96 (dd, *J* = 1.4, 15.4 Hz, 1 H, C*H*CHCH$_3$), 5.45 (qd, J = 6.6, 15.1 Hz, 1 H, CHC*H*CH$_3$), 3.83 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 1.76 (dd, *J* = 1.3, 6.6 Hz, 3 H, CHCHC*H*$_3$), 1.71 (d, *J* = 1.1 Hz, 3 H, EtOCHC*H*$_3$), 1.27 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$). (*1E, 3Z*): ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.15 - 6.07 (m, 1 H, C*H*OEt), 5.70 (app d, *J* = 11.3 Hz, 1 H, C*H*CHCH$_3$), 5.31 (qd, *J* = 7.2, 11.7 Hz, 1 H, CHC*H*CH$_3$), 3.83 (q, *J* = 7.0 Hz, 2 H, C*H*$_2$CH$_3$), 1.76 (dd, *J* = 1.3, 6.6 Hz, 3 H, CHCHC*H*$_3$), 1.69 (d, *J* = 1.1 Hz, 3 H, EtOCHC*H*$_3$), 1.28 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ 145.4, 130.8, 119.5, 114.3, 67.9, 18.3, 15.3, 9.6. I.R (thinfilm) $_v$max (cm^{-1}): 2978 (C=C-H), 2932 (C=C-H), 1650 (C=C), 1634 (C=C)

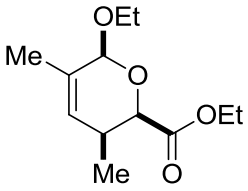
Synthesis of BINOL-Ti complex 106.3[242]



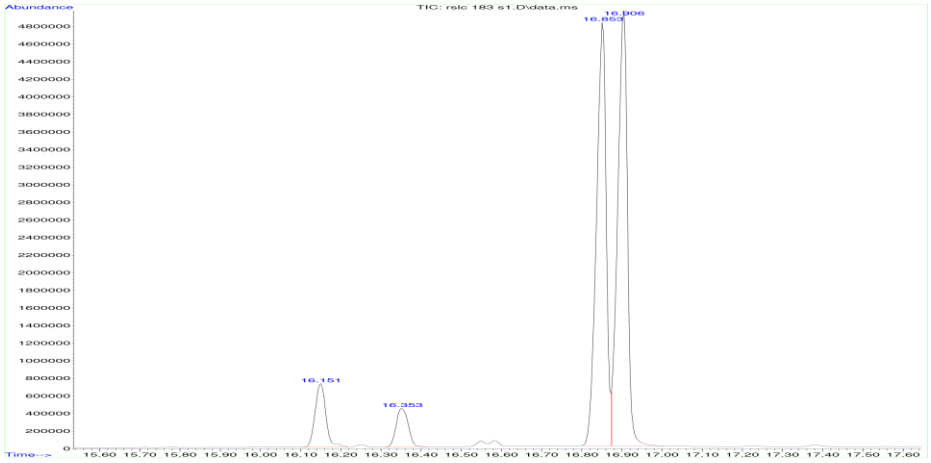
A 250 mL Schlenk tube was charged with powdered molecular sieves 4Å (15.0 g) and *(R)*-(+)-binaphthol (0.859 g, 3.0 mmol). The Schlenk was then transferred into a glovebox where anhydrous CH_2Cl_2 (90 mL) was added and the reaction was stirred for 20 min. Diisopropoxytitanium(IV) chloride (0.711 g, 3.0 mmol) was added in one portion resulting in a

red brown reaction mixture. The reaction was removed from the glove box and allowed to stir at rt for 1 h. The reaction mixture was then allowed to settle overnight. The reaction solution was transferred *via* cannula into a new Schlenk flask leaving the molecular sieves behind. The stirred reaction was evaporated at 0 °C under reduced pressure to afford a deep red/brown residue. The resulting residue is suspended in anhydrous pentane (50 mL) and stirred for 20 min. The pentane was decanted *via* syringe and the resulting precieptate was vacuum-dried to give the binaphthol-titanium complex in 90-95% yield and used as catalyst in subsequent reactions.

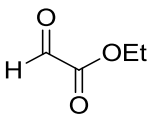
Synthesis of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate 104.2



CH_2Cl_2 (3.0 mL) was added to binaphthol-titanium complex **106.3** (0.016 g, 0.04 mmol) under a N_2 environment. Ethyl glyoxalate 50% in toluene (0.32 mL, 1.6 mmol) was added and the reaction cooled to -30 °C. (*1E,3E*)-1-ethoxy-2-methylpenta-1,3-diene **96.1** (0.1 g, 0.8 mmol) was added and the reaction was stirred at -30 °C for 4 h. The reaction was concentrated *in vacuo* to give a crude mixture which was purified by column chromatography (15% EtOAc in pentane Rf = 0.7) the fractions containing product were combined and concentrated *in vacuo* to give the title compound as a clear oil (0.118 g, 65%, 0.52 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.71 - 5.68 (m, 1 H, C=C*H*), 5.09 (s, 1 H, EtOC*H*), 4.34 (d, *J* = 3.5 Hz, 1 H, C*H*$CO_2CH_2CH_3$), 4.28 - 4.22 (m, 2 H, $CO_2CH_2CH_3$), 3.87 (dq, *J* = 9.6, 7.0 Hz, 1 H, OC*H*a$H_b$$CH_3$), 3.66 (dq, *J* = 9.5, 7.1 Hz, 1 H, OCHa*H*$_b$$CH_3$), 2.48 - 2.42 (m, 1 H, C*H*CH_3), 1.66 (s, 3 H, C*H*$_3$C=C), 1.30 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.25 (t, *J* = 7.1 Hz, 3 H, OCHaH_bC*H*$_3$), 1.01 (d, *J* = 6.9 Hz, 3 H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.0, 132.9, 129.3, 100.3, 74.1, 62.8, 60.8, 31.7, 17.5, 15.2, 14.7, 14.3. I.R (thin film) ν max (cm^{-1}): 2975 (C=C-H), 1759 (C=O), 1730 (C=C). HRMS (ESI): m/z calculated. $C_{12}H_{20}O_4$: requires 251.1259 for $[M+Na]^+$; found: 251.1264.

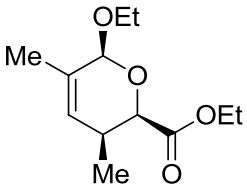


Purification of ethyl glyoxalate



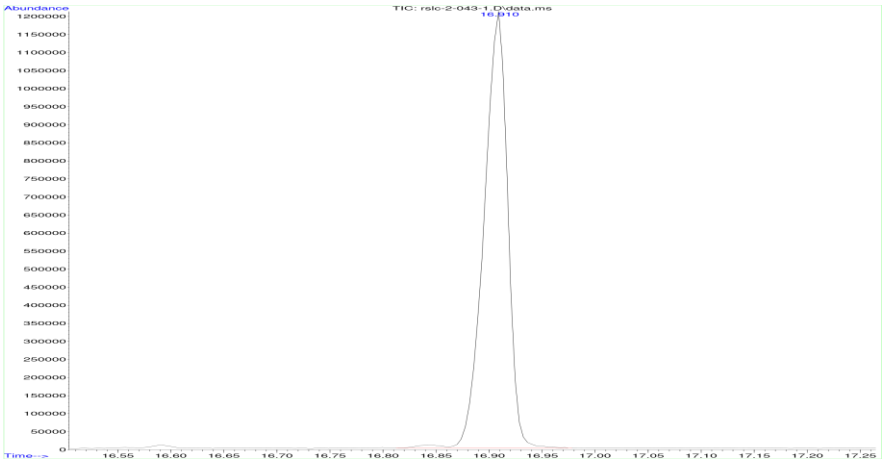
Commercially available ethyl glyoxalate 50% in toluene was concentrated to remove the toluene. The remaining glyoxalate is then distilled under reduced pressure to afford pure ethyl glyoxalate. The collection vessel is kept at -78 °C for the duration of the distillation. The pure ethyl glyoxalate was then diluted to a 50% solution with fresh anhydrous CH_2Cl_2 and transferred to a Schlenk flask. Allowing for freezer storage of the pure ethyl glyoxalate.

Synthesis of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate 104.2

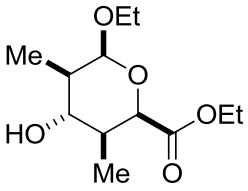


CH_2Cl_2 (3.0 mL) was added to binaphthol-titanium complex **106.3** (0.016 g, 0.04 mmol) under a N_2 environment, ethyl glyoxalate 50% in CH_2Cl_2 (0.32 mL, 1.6 mmol) was added and the reaction cooled to -30 °C. (*1E,3E*)-1-ethoxy-2-methylpenta-1,3-diene **96.1** (0.1 g, 0.8 mmol) was added and the reaction was stirred at -30 °C for 4 h. The reaction was concentrated *in vacuo* to give a crude mixture which was purified by column chromatography (15% EtOAc in pentane Rf = 0.7). The fractions containing product were combined and concentrated *in vacuo* to give the title compound as a clear oil (0.118 g, 65%), $[\alpha]_D^{20}$ = +114 (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.71 - 5.68 (m, 1 H, C=C*H*), 5.09 (s, 1 H, EtOC*H*), 4.34 (d, *J* = 3.5 Hz, 1 H, C*H*$CO_2CH_2CH_3$), 4.28 -

4.22 (m, 2 H, $CO_2CH_2CH_3$), 3.87 (dq, *J* = 9.6, 7.0 Hz, 1 H, $OCHaH_bCH_3$), 3.66 (dq, *J* = 9.5, 7.1 Hz, 1 H, $OCHaH_bCH_3$), 2.48 - 2.42 (m, 1 H, $CHCH_3$), 1.66 (s, 3 H, $CH_3C{=}C$), 1.30 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.25 (t, *J* = 7.1 Hz, 3 H, $OCHaH_bCH_3$), 1.01 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 132.9, 129.3, 100.3, 74.1, 62.8, 60.8, 31.7, 17.5, 15.2, 14.7, 14.3. I.R (thin film) $_{v}$max (cm^{-1}): 2975 (C=C-H), 1759 (C=O), 1730 (C=C). HRMS (ESI): m/z calculated. $C_{12}H_{20}O_4$: requires 251.1259 for $[M+Na]^+$; found: 251.1264.



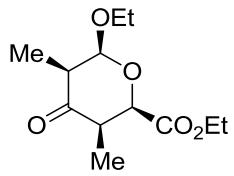
Synthesis of ethyl 6-ethoxy-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate 110.1



Borane dimethyl sulfide complex (0.2 mL, 1.75 mmol) was added dropwise to a stirred solution of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate **27.3** (0.2 g, 0.87 mmol) in THF (5 mL) at -5 °C the reaction was then placed in a freezer at -20 °C for 16 h. The reaction was warmed to -5 °C followed by the addition of H_2O_2 (30 % w/w) (0.548 mL) and NaOH (0.2 g, 4.35 mmol) the reaction was stirred for a further 1 h. The reaction was diluted with H_2O (10 mL) and Et_2O (20 mL) the layers were separated and the organics were washed with H_2O (10 mL X 3), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified *via* column chromatography (20% EtOAc in pentane Rf = 0.3). The fractions containing product were combined and concentrated *in vacuo* to give the title compound as a clear oil (0.18 g, 85%, 0.74 mmol). $[\alpha]_D^{20}$ = +21 (MeOH). ^1H NMR (500 MHz, $CDCl_3$) δ 4.76 (d, J = 3.5 Hz, 1H, EtOC*H*), 4.31 (d, *J* = 4.4 Hz, 1H, $CHCO_2CH_2CH_3$), 4.24 (dq, *J* = 10.8, 7.1 Hz, 1H, $CO_2CHaH_bCH_3$), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H, $CO_2CHaH_bCH_3$), 3.93 (t, *J* = 7.4 Hz, 1H, C*H*OH), 3.83 (dq, *J* =9.8, 7.0 Hz, 1H, $OCHaH_bCH_3$, 3.45 (dq, *J* = 9.8, 7.0 Hz, 1H, $OCHaH_bCH_3$), 1.99 (app quin d, *J* = 7.3, 4.6 Hz, 1H, $CH(CO_2Et)CHCH3$),

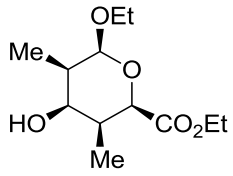
1.79 (app quin d, *J* = 7.2, 3.5 Hz, 1H, CH(OEt)C*H*CH_3), 1.70 (br. s, 1H, OH), 1.30 (t, *J* = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.18 - 1.11 (m, 6H, OCH_2CH_3 and EtOCHCH_3), 1.04 (d, *J* = 6.9 Hz, 3H, CH(CO_2Et)CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.7, 102.3, 74.2, 72.5, 64.7, 60.6, 42.1, 39.6, 14.7, 14.2, 12.7, 12.1. I.R (thin film) ν max (cm^{-1}): 3505 (OH), 1736 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{22}O_5$: requires: 269.1365 for $[M+Na]^+$; found: 269.1355.

Synthesis of ethyl 6-ethoxy-3,5-dimethyl-4-oxotetrahydro-2H-pyran-2-carboxylate 111.1



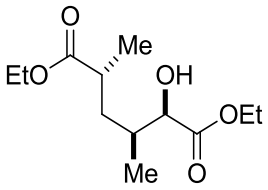
Oxalyl chloride (0.056 g, 0.44 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL) at -55 °C under N_2. DMSO (0.062 g, 0.80 mmol) was added and the resulting solution was stirred for 2 min. 6-ethoxy-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate (0.10 g, 0.40 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the solution to form a light yellow cloudy mixture, which was stirred for a further 15 mins at -55 °C. NEt_3 (0.26 mL, 2.0 mmol) was then added and the resulting solution was stirred for 15 mins at -55 °C. The white slurry was then allowed to warm to rt and was quenched with H_2O (10 mL). The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2 (20 mL). The organics were combined and washed with 1 M HCl and saturated $NaHCO_3$, before being dried ($MgSO_4$) and concentrated under vacuum. The resulting residue was purified by column chromatography (5% EtOAc in pet ether). The fractions containing product were combined and concentrated under vacuum to give the title compound as a waxy oil (0.079 g, 80%, 0.32 mmol). ^{1}H NMR (300 MHz, $CDCl_3$)) δ 5.1 (d, *J* = 4.0 Hz, 1H, OC*H*OCH_2CH_3), 4.7 (d, *J* = 4.9 Hz, 1H, C*H*C(O)OCH_2CH_3), 4.2 (q, *J* = 7.1 Hz, 2H, CHC(O)OCH_2CH_3), 3.9 (dq, *J* = 9.7, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.5 (dq, *J* = 9.7, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 2.9 – 2.8 (m, 2H, 2 x C*H*CH_3), 1.3 (t, *J* = 7.2 Hz, 3H, CHC(O)OCH_2CH_3), 1.2 – 1.1 (m, 6H, OCH_2CH_3 and CHCH_3), 1.1 (d, *J* = 6.8 Hz, 3H, CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$)) δ 207.5, 169.7, 102.8, 75.3, 64.5, 61.3, 47.9, 45.5, 14.8, 14.2, 11.6, 9.6. I.R (thin film) $_\nu$max (cm^{-1}): 2979, 2936 (C-H), 1727 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{20}O_5$: requires: 267.1208 for $[M+Na]^+$; found: 267.1259.

Synthesis of (2R,3S,4R,5R,6S)-ethyl 6-ethoxy-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate 111.2



Sodium borohydride (0.011 g, 0.30 mmol) was added to a stirred solution of ethyl 6-ethoxy-3,5-dimethyl-4-oxotetrahydro-2H-pyran-2-carboxylate (0.065 g, 0.266 mmol) in EtOH (5 mL) at 0 °C under a N_2 environment. The reaction was allowed to reach rt and stirred for 1 h, the reaction was concentrated under vacuum. The resulting residue was partitioned between CH_2Cl_2 and H_2O, the layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (20 mL x 2), the organics were combined dried ($MgSO_4$) and concentrated under vacuum to give the title compound as a clear oil (0.062 g, 95%, 0.25 mmol). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.6 (d, *J* = 3.4 Hz, 1H, OC*H*OCH$_2$CH$_3$), 4.3 – 4.2 (m, 1H, C(O)OC*H*$_a$H$_b$CH$_3$), 4.2 (d, *J* = 5.8 Hz, 1H, C*H*C(O)OCH$_2$CH$_3$), 4.2 – 4.1 (m, 1H, C(O)OCH$_a$*H*$_b$CH$_3$), 3.8 (dq, *J* = 9.7, 7.1 Hz, 1H, OC*H*$_a$H$_b$CH$_3$), 3.7 – 3.6 (m, 1H, C*H*OH), 3.4 (dq, *J* = 9.7, 7.0 Hz, 1H, OCH$_a$*H*$_b$CH$_3$), 2.2 (qdd, *J* = 7.3, 5.7, 3.7 Hz, 1H, C*H*(CH$_3$)CHOH), 1.9 (qt, *J* = 7.2, 3.6 Hz, 1H, C*H*(CH$_3$)CHC(O)OCH$_2$CH$_3$), 1.3 (td, *J* = 7.1, 0.6 Hz, 3H, C(O)OCH$_2$C*H*$_3$), 1.2 – 1.1 (m, 6H, OCH$_2$C*H*$_3$ and CHC*H*$_3$), 1.1 – 1.0 (m, 3H, CHC*H*$_3$). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.0, 101.3, 73.6, 70.6, 64.7, 61.2, 39.2, 37.0, 14.8, 14.3, 12.7, 12.3. I.R (thin film) ν max (cm^{-1}): 3480 (OH), 1739 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{22}O_5$: requires: 269.1365 for [M+Na]$^+$; found: 269.1362.

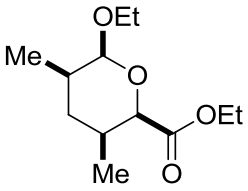
Synthesis of diethyl 2-hydroxy-3,5-dimethylhexanedioate 112.1



5% Pd/AlO$_3$ (0.18 g, 0.088 mmol) was added to a solution of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.2 g, 0.87 mmol) in EtOH (3 mL) the reaction when then placed under a H_2 environment and stirred at rt for 24 h. The reaction was filtered through Celite® and concentrated *in vacuo*. The residue was purified *via* column chromatography (20% EtOAc in pentane Rf = 0.15). The fractions containing product were combined and concentrated *in vacuo* to give the title compound as a clear oil (0.16 g, 75%, 0.066 mmol). ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.34 - 4.20 (m, 2H, CH(CH$_3$)CO$_2$C*H*$_2$CH$_3$), 4.19 - 4.05 (m, 3H, CH(OH)CO$_2$C*H*$_2$CH$_3$ and

C*H*(OH)$CO_2CH_2CH_3$), 2.79 (d, *J* = 5.3 Hz, 1H, $CO_2EtCHCH_3$), 2.63 - 2.46 (m, 1H, CH(OH)C*H*CH_3), 2.08 - 1.93 (m, 1H, $CH(CH_3)CH_aCH_bCH(CH_3)$), 1.92 - 1.80 (m, 1H, $CH(CH_3)CH_aCH_bCH(CH_3)$), 1.29 (t, *J* = 7.2 Hz, 3H, CH(OH)$CO_2CH_2CH_3$), 1.26 (t, J = 7.2 Hz, 3H, $CH(CH_3)CO_2CH_2CH_3$), 1.19 (d, *J* = 7.0 Hz, 3H, CH(OH)$CHCH_3$), 0.83 (d, *J* = 6.6 Hz, 3H, $CO_2EtCHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 174.8, 73.3, 61.7, 60.2, 37.3, 37.2, 34.5, 17.9, 14.2, 14.2, 12.9. I.R (thin film) ν max (cm^{-1}): 3505 (OH), 1727 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{22}O_5$: requires: 269.1365 for $[M+Na]^+$; found: 269.1431.

Synthesis of ethyl 6-ethoxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate 112.2



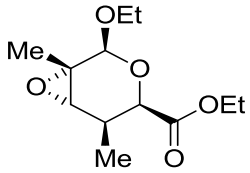
5% Pd/AlO_3 (0.18 g, 0.088 mmol) was added to a solution of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate **27.3** (0.2 g, 0.87 mmol) in EtOAc (3 mL), the reaction was then placed under a pressurised H_2 environment (50 PSI) and stirred at rt for 24 h. The reaction was filtered through Celite® and concentrated *in vacuo*. The residue was purified *via* column chromatography (20% EtOAc in pentane Rf = 0.4). The fractions containing product were combined and concentrated *in vacuo* to give the title compound as a clear oil (0.17 g, 85%, 0.075 mmol). $[\alpha]_D^{20}$ = +48 (MeOH), +82 ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (d, *J* = 3.2 Hz, 1H, EtOC*H*), 4.24 (qd, *J* = 7.1, 10.8 Hz, 1H, $OCH_aH_bCH_3$), 4.18 - 4.08 (m, 1H, $OCH_aH_bCH_3$), 4.04 (d, *J* = 4.7 Hz, 1H, C*H*$CO_2CH_2CH_3$), 3.82 (dq, *J* = 9.8, 7.1 Hz, 1H, $CO_2CH_aH_bCH_3$), 3.45 (dq, *J* = 9.8, 7.0 Hz, 1H, $CO_2CH_aH_bCH_3$), 2.10 - 2.01 (m, 1H, $CH(CO_2Et)CHCH_3$), 1.90 - 1.84 (m, 1H, CH(OEt)C*H*CH_3), 1.84 - 1.75 (m, 1H, $CH(CH_3)CH_aCH_bCH(CH_3)$), 1.56 - 1.49 (m, 1H, $CH(CH_3)CH_aCH_bCH(CH_3)$), 1.31 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 1.15 (t, *J* = 6.9 Hz, 3H, OCH_2CH_3), 1.09 (d, *J* = 7.3 Hz, 3H, CH(OEt)$CHCH_3$), 0.94 (d, *J* = 6.6 Hz, 3H, $CH(CO_2Et)CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 101.6, 73.9, 64.3, 60.3, 34.5, 32.2, 31.6, 16.9, 16.1, 14.7, 14.2. I.R (thin film) ν max (cm^{-1}): 1739 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{22}O_4$: requires: 253.1416 for $[M+Na]^+$; found: 253.1407.

Preparation of quaternary ammonium tetrakis(diperoxotungsto)phosphates (-3) $[(C_8H_{17})_3NCH_3]_3PO_4[W(O)(O_2)_2]_4$[266]

Tungstic acid (2.5 g, 10.0 mmol) was suspended in 30% H_2O_2 (7 mL) and heated at 60 °C until the reaction becomes a clear solution. The reaction was then cooled to rt, 40% phosphoric acid (0.62 mL, 2.5 mmol) was added and the reaction was diluted to 30 mL with H_2O. Aliquat 336 (2.29 mL,

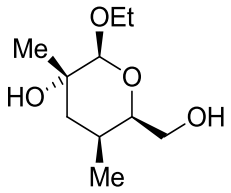
5 mmol) in CH_2Cl_2 (40 mL) was then added to the reaction and stirred at rt for 15 min. The organic layer was then separated, dried (Na_2SO_4) and concentrated to give the title compound as a clear viscous oil. Used without further purification.

Synthesis of ethyl 2-ethoxy-1,5-dimethyl-3,7-dioxabicyclo[4.1.0]heptane-4-carboxylate 116.1



Ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.2 g, 0.87 mmol) was added to a mixture of $[(C_8H_{17})_3NCH_3]_3PO_4[W(O)(O_2)_2]_4$ (0.028 g, 0.0087 mmol) in 30% H_2O_2 (0.155 mL, 0.96 mmol) neutralised with 1 drop of 2M NaOH. The reaction was stirred at rt for 4 h. The reaction was diluted with $NaHCO_{3(aq)}$ (20 mL) and a Et_2O/Pentane mix (10 mL 1:1). The layers were separated and the aqueous layer is further extracted with Et_2O/Pentane 1:1 mix (3 X 10 mL). The organic layers were then combined, dried ($MgSO_4$) and concentrated under vacuum to give pure title compound as a colourless oil in 95% yield (0.201 g, 0.83 mmol). $[\alpha]_D^{20}$ = +62.5 (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.8 (dd, *J* = 1.3, 0.5 Hz, 1H, EtOC*H*O), 4.2 (d, *J* = 3.3 Hz, 2H, OC*H*C(O)OEt), 4.2 (qd, *J* = 7.1, 2.4 Hz, 3H, C(O)OCH_2CH$_3$), 4.0 (dq, *J* = 9.6, 7.1 Hz, 1H, OCH_aH$_b$CH$_3$), 3.6 (dq, *J* = 9.6, 7.0 Hz, 1H, OCH$_a$$H_bCH_3$), 3.0 (dd, *J* = 2.7, 1.2 Hz, 1H, C(CH$_3$)OC*H*), 2.6 – 2.5 (m, 1H, C*H*CH$_3$), 1.3 (s, 3H, C(CH_3)OCH), 1.3 (t, *J* = 7.2 Hz, 3H, C(O)OCH$_2$CH_3), 1.2 (t, *J* = 7.0 Hz, 3H, OCH$_a$H$_b$CH_3), 1.0 (d, *J* = 7.1 Hz, 3H, CHCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 100.2, 69.7, 65.5, 63.0, 61.0, 58.2, 32.0, 18.6, 15.2, 14.4, 10.9. I.R (thin film) $_v$max (cm^{-1}): 2977, 2935 (C-H), 1758 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{20}O_5$: requires: 245.1388 for $[M+H]^+$; found: 245.1370.

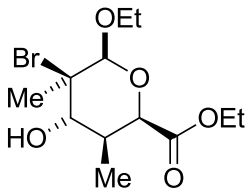
Synthesis of 2-ethoxy-6-(hydroxymethyl)-3,5-dimethyltetrahydro-2H-pyran-3-ol 118.1



2-ethoxy-1,5-dimethyl-3,7-dioxabicyclo[4.1.0]heptane-4-carboxylate (0.1 g, 0.41 mmol) in anhydrous THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.063 g, 0.82 mmol) in anhydrous THF (5 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and then poured into a saturated solution of NH_4Cl (20 mL). The reaction was extracted with Et_2O (3 x 20 mL), the organic layers were combined, dried ($MgSO_4$) and concentrated under vacuum to give pure title

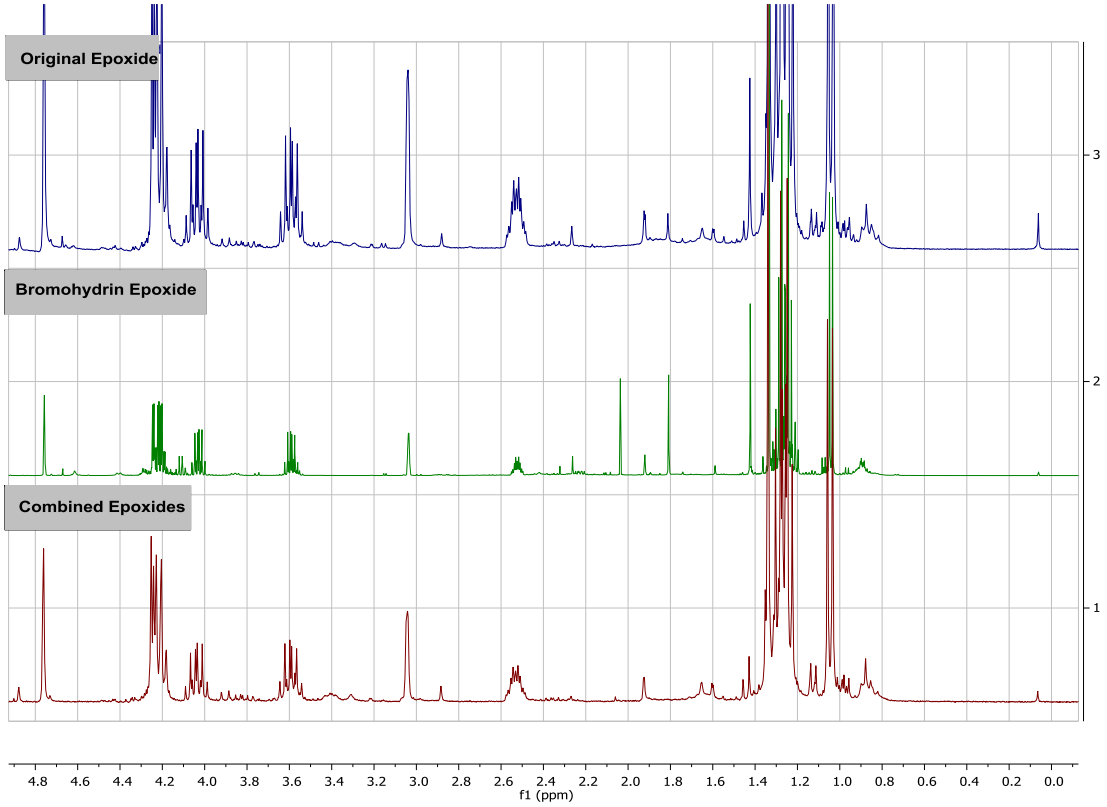
compound as a pale yellow oil in 90% yield (0.075 g, 0.37 mmol). $[\alpha]_D^{20}$ = +44 (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.8 (d, *J* = 1.0 Hz, 1H, OC*H*OCH_2CH_3), 4.0 (dq, *J* = 9.7, 7.1 Hz, 1H, OCHOC*H*$_a$H$_b$$CH_3$), 3.7 – 3.5 (m, 4H, OCHOCH_a*H*$_b$$CH_3$, OC*H*$CH_2$OH and OCHC*H*$_2$OH), 2.9 (dd, *J* = 2.0, 1.1 Hz, 1H, C*H*$_a$H$_b$CHCH$_3$), 2.3 (s, 1H, CH$_a$*H*$_b$CHCH$_3$), 2.2 – 2.1 (m, 1H, CH$_a$H$_b$C*H*CH_3), 1.3 (s, 3H, C(OH)C*H*$_3$), 1.3 (t, *J* = 7.1 Hz, 3H, CH_2C*H*$_3$), 1.0 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.6, 71.3, 65.4, 63.5, 63.4, 57.7, 30.8, 18.7, 15.3, 11.4. I.R (thin film) $_v$max (cm^{-1}): 3446 (OH), 2974, 2931 (C-H). HRMS (ESI): m/z calculated. $C_{10}H_{20}O_4$: requires: 205.1440 for $[M+H]^+$; found: 205.1431.

Synthesis of ethyl 5-bromo-6-ethoxy-4-hydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate 119.1



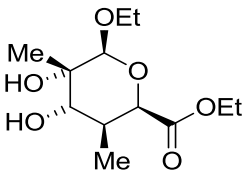
NBS (0.052 g, 0.43 mmol) was added to a mixture of ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.1 g, 0.43 mmol) in acetone/H_2O 1:1 (6 mL). The reaction was stirred at 10 °C for 2 h and then concentrated under vacuum. The residue was dissolved in EtO_2 (30 mL) and washed with $NaHCO_{3(aq)}$ (3 x 20 mL). The organics were dried ($MgSO_4$) and concentrated under vacuum to give the crude product. The residue was purified *via* column chromatography (20% EtOAc in pentane Rf = 0.2) the fractions containing product were combined and concentrated *in vacuo* to give the title compound as a white solid (0.11 g, 86%, 0.37 mmol). $[\alpha]_D^{20}$ = +38 (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.6 (s, 1H, OC*H*OCH_2CH_3), 4.4 (d, *J* = 8.3 Hz, 1H, OC*H*C(O) OCH_2CH_3), 4.3 – 4.3 (m, 1H, *CHOH*), 4.3 – 4.1 (m, 2H, C(O)C*H*$_2$$CH_3$), 3.9 – 3.8 (m, 1H, OC*H*$_a$H$_b$$CH_3$), 3.6 (dq, *J* = 9.8, 7.0 Hz, 1H, OCH$_a$*H*$_b$$CH_3$), 2.3 – 2.2 (m, 1H, C*H*CH_3), 2.2 (d, *J* = 3.4 Hz, 1H, O*H*), 1.8 (s, 3H, C(Br)C*H*$_3$), 1.3 (t, *J* = 7.2 Hz, 3H C(O)OCH_2C*H*$_3$), 1.3 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 1.2 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 103.9, 74.2, 65.9, 60.7, 51.4, 37.2, 23.8, 14.5, 14.3 14.2, 13.7. I.R (thin film) ν max (cm^{-1}): 3467 (OH), 2971, 2942 (C-H), 1726 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{21}BrO_5$: requires: 347.0470 for $[M+Na]^+$; found: 347.0473.

NMR experiment to show that the epoxide formed from bromohydrin ring closure is the same as the epoxide formed directly from dihydropyran **104.2**



Comparison of epoxide ^{1}H NMR

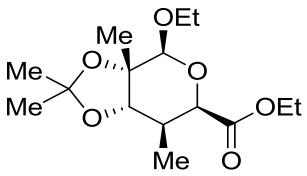
Synthesis of ethyl 6-ethoxy-4,5-dihydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate 122.1



AD-mix-α (or AD-mix-β) (1.4 g) was dissolved in 1:1 *tert*-butanol:water (10 mL) and stirred at rt to produce two clear phases. Methanesulfonamide (0.095 g, 1.0 mmol) was added and the reaction was cooled to 0 °C. Ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.22 g, 1.0 mmol) was then added and the reaction was vigorously stirred at 0 °C for 4 d. Sodium sulphite was added and the reaction was allowed to warm to rt and stirred for a further 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organics were combined, washed with 2 M $KOH_{(aq)}$, dried ($MgSO_4$) and concentrated under vacuum. The resulting residue was purified *via* column chromatography (20% EtOAc in pentane Rf = 0.3) to give the title compound as a clear oil (0.118 g, 45%, 0.45 mmol) $[\alpha]_D^{20}$ = +32 MeOH. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.6 (s, 1H, C*H*CH_2CH_3), 4.6 (d, *J* = 3.6 Hz, 1H, OC*H*C(O) OCH_2CH_3), 4.2 (qt, *J* = 6.9, 3.5 Hz, 2H, C(O)C*H*$_2$$CH_3$), 4.0 (dq, *J* = 9.7, 7.1 Hz, 1H, OC*H*$_a$$H_b$$CH_3$), 3.7 (d, *J* = 3.5 Hz, 1H, C*H*OH),

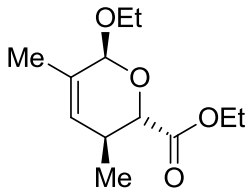
3.5 (dq, *J* = 9.6, 7.0 Hz, 1H, $OCH_aH_bCH_3$), 2.4 (qt, *J* = 7.5, 3.6 Hz, 1H, $CHCH_3$), 1.3 – 1.3 (m, 6H, $C(OH)CH_3$ and $C(O)CH_2CH_3$), 1.2 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.0 (d, *J* = 7.6 Hz, 3H, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 103.1, 77.3, 73.8, 71.4, 65.6, 61.0, 37.4, 20.5, 15.1, 14.4, 13.0. I.R (thin film) ν max (cm^{-1}): 3473 (OH), 2979, 2933 (C-H), 1737 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{22}O_6$: requires: 285.1314 for $[M+Na]^+$; found: 285.1290.

Synthesis of ethyl 4-ethoxy-2,2,3a,7-tetramethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-carboxylate 123.1



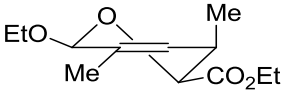
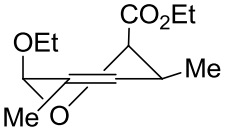
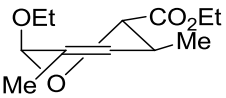
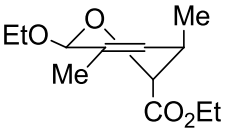
p-Toluenesulfonic acid (0.001 g, 0.0053 mmol) was added to a stirred solution of ethyl 6-ethoxy-4,5-dihydroxy-3,5-dimethyltetrahydro-2H-pyran-2-carboxylate (0.03 g, 0.11 mmol) in 2,2-dimethoxypropane (2 mL) and acetone (2 mL). The reaction was stirred at rt for 2 h, the reaction was then concentrated under vacuum, dissolved in Et_2O and extracted with saturated Na_2CO_3. The organics were dried ($MgSO_4$) and concentrated under vacuum to give the title compound as a pale yellow solid (0.031 g, 95%, 0.0050 mmol), mpt = 56-59 °C, $[\alpha]_D^{20}$ = +57 MeOH. ^1H NMR (300 MHz, $CDCl_3$) δ 4.5 – 4.4 (m, 2H, $OCHOCH_2CH_3$ and $CHC(O)OCH_2CH_3$), 4.2 (q, *J* = 7.2 Hz, 2H, $CHC(O)OCH_2CH_3$), 4.0 (dq, *J* = 9.4, 7.1 Hz, 1H, $OCH_aH_bCH_3$), 3.8 (d, *J* = 1.8 Hz, 1H, $CHOC(CH_3)_2$), 3.6 (dq, *J* = 9.4, 7.0 Hz, 1H, $OCH_{aHb}CH_3$), 2.5 (qdd, *J* = 7.5, 3.1, 1.8 Hz, 1H, $CHCH_3$), 1.5 (s, 3H, $CH_3C(O)C(O)$), 1.4 (s, 3H, $OC(CH_3)_a(CH_3)_bO$), 1.3 (s, 3H, $OC(CH_3)_a(CH_3)_bO$), 1.3 – 1.2 (m, 3H, $C(O)OCH_2CH_3$), 1.3 – 1.2 (m, 3H, OCH_2CH_3), 1.0 (d, *J* = 7.5 Hz, 3H, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 108.1, 104.6, 84.5, 78.4, 73.6, 65.7, 61.2, 33.8, 28.5, 26.9, 17.7, 15.0, 14.4, 12.3. I.R (thin film) ν max (cm^{-1}): 2979, 2933, 2879 (C-H), 1753 (C=O). HRMS (ESI): m/z calculated. $C_{15}H_{26}O_6$: requires: 325.1627 for $[M+Na]^+$; found: 325.1657.

Synthesis of (2S,3S,6S)-ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate 104.3

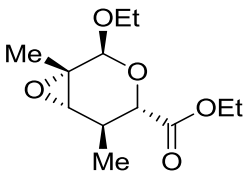


Potassium *tert*-butoxide (0.02 g, 0.16 mmol) in THF (0.5 mL) was added dropwise to a stirred solution of (2R,3S,6S)-ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.20 g, 0.8 mmol) in THF (4 mL) at 0 °C. The reaction as stirred at 0 °C for 2 h, 1 M $NaHSO_{4(aq)}$ (0.4 mL) was added and the reaction was warmed to rt. The reaction was diluted with Et_2O (20 mL) and extracted with H_2O and brine. The aqueous layers were extracted with Et_2O, the organics were combined, dried ($MgSO_4$) and concentrated under vacuum to give the title compound as a clear oil (0.192 g, 96%, 0.77 mmol). $[\alpha]_D^{20}$ = +20.5 MeOH. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.4 (d, *J* = 2.3 Hz, 1H, C=C*H*), 4.8 (s, 1H, OC*H*OCH_2CH_3), 4.3 (q, *J* = 7.1 Hz, 2H, C(O)OCH_2CH_3), 4.0 (d, *J* = 10.4 Hz, 1H, *CHC*(O)OCH_2CH_3) 3.8 (dq, *J* = 9.9, 7.1 Hz, 1H, $CH_aH_bCH_3$), 3.6 (dq, *J* = 9.8, 7.1 Hz, 1H, $CH_aH_bCH_3$), 2.5 (ddtt, *J* = 9.2, 5.6, 2.1, 1.1 Hz, 1H, C*H*CH_3), 1.7 (q, *J* = 1.9 Hz, 3H, CH_3C=C), 1.3 (t, *J* = 7.1 Hz, 3H, C(O)OCH_2CH_3), 1.2 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.0 (d, *J* = 7.1 Hz, 3H, CHCH_3). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 171.2, 131.5, 128.6, 97.3, 72.9, 64.3, 61.2, 32.4, 18.8, 16.7, 15.4, 14.4. I.R (thin film) $_{\nu}$max (cm^{-1}): 2974, 2876 (C-H), 1740 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{20}O_4$: requires 251.1259 for $[M+Na]^+$; found: 251.1263.

Computational results

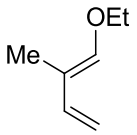
Entry	Compound	I/TS	Description	G/Hartrees	ΔG (kcal/mol)
1		I	CO_2Et up, eq.	-770.177310	2.3
2		I	CO_2Et up, ax.	-770.173262	4.8
3		I	CO_2Et down, eq.	-770.180908	0
4		I	CO_2Et down, ax.	-770.177082	2.4

Synthesis of ethyl 2-ethoxy-1,5-dimethyl-3,7-dioxabicyclo[4.1.0]heptane-4-carboxylate 128.1



Ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.1 g, 0.44 mmol) was added to a mixture of $[(C_8H_{17})_3NCH_3]_3PO_4[W(O)(O_2)_2]_4$ (0.014 g, 0.0044 mmol) in 30% H_2O_2 (0.078 mL, 0.48 mmol) neutralised with 1 drop of 2M NaOH. The reaction was stirred at rt for 4 h. The reaction was diluted with $NaHCO_{3(aq)}$ (20 mL) and a Et_2O/Pentane mix (10 mL 1:1). The layers were separated and the aqueous layer is further extracted with Et_2O/Pentane 1:1 mix (3x 10 mL). The organic layers were then combined, dried ($MgSO_4$) and concentrated under vacuum to give pure title compound as a colourless oil in a 96% yield (0.101 g, 0.42 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.9 (s, 1H, C*H*OCH_2CH_3), 4.2 (q, *J* = 7.2 Hz, 2H, C(O)OC*H*$_2$$CH_3$), 3.9 (d, *J* = 10.4 Hz, 1H, OC*H*$_a$H$_b$$CH_3$), 3.8 (dt, *J* = 9.8, 7.1 Hz, 1H, C*H*C(O)OCH_2CH_3), 3.6 (dq, *J* = 9.8, 7.0 Hz, 1H, OCH$_a$*H*$_b$$CH_3$), 2.9 (s, 1H, C*H*O (epoxide)), 2.4 – 2.2 (m, 1H, C*H*CH_3), 1.3 (s, 3H, CO(C*H*$_3$)), 1.3 (dt, *J* = 13.2, 7.2 Hz, 6H, CHOCH$_2$C*H*$_3$ and C(O)OCH$_2$C*H*$_3$), 1.1 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 97.7, 70.3, 64.5, 62.0, 61.4, 55.1, 30.8, 18.0, 15.8, 15.2, 14.3. I.R (thin film) ν max (cm^{-1}): 2985, 2940 (C-H), 1731 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{20}O_5$: requires: 245.1388 for $[M+H]^+$; found: 245.1370.

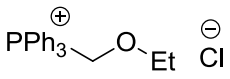
Synthesis of (*E*)-1-ethoxy-2-methylbuta-1,3-diene 130.1



nBuLi (14.7 mL, 1.4 M in hexanes) was added slowly to a stirred solution of diisopropylamine (4.16 mL, 28.8 mmol) in THF (50 mL) at -78 °C and stirred for 10 min. The reaction was then warmed to 0 °C followed by the addition of methyltriphenylphosphonium bromide 8.93 g, 25.0 mmol) the reaction was then allowed to warm to rt and stirred for 1 h. (*E*)-3-ethoxy-2-methylacrylaldehyde **20.2** (2.35 g, 20.6 mmol) was added dropwise and stirred for 2 h. The reaction was then diluted with H_2O (100 mL) and extracted with Et_2O (3x 50 mL), the combined organic layers were dried ($MgSO_4$) and carefully concentrated *in vacuo* to give a crude mixture of product and triphenylphosphine oxide. The product was purified by distillation under reduced pressure to give the title compound as a clear oil (1.61 g, 70%, 14.42 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.3 (dd, *J* = 17.2, 10.7 Hz, 1H, C*H*=CH_2), 6.2 (s, 1H, C*H*OCH_2CH_3), 5.0 (ddd, *J* =

17.2, 1.4, 0.7 Hz, 1H, CH=CH_aH$_b$), 4.8 (dd, *J* = 10.7, 1.4 Hz, 1H, CH=CH$_a$$H_b$), 3.9 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 1.7 (d, *J* = 1.3 Hz, 3H, CH_3C=C), 1.3 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 137.0, 114.7, 107.9, 68.3, 15.5, 9.0. I.R (thinfilm) $_v$max (cm^{-1}): 2980, 2939, 2880 (C=C-H), 1651 (C=C).

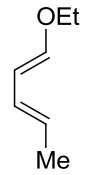
Synthesis of (ethoxymethyl)triphenylphosphonium chloride



Triphenylphosphine (20.0 g, 0.076 mol) and chloromethyl ethyl ether (7.9 g, 0.084 mol) were dissolved in CH_2Cl_2 and heated at 42 °C for 12 h. The reaction was concentrated under vacuum, the solid residue was washed with pet ether to give the title compound as a white solid (27.0 g, 99%, 0.0752 mol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (s, 9H, ArH), 7.6 (dddq, *J* = 7.7, 6.2, 3.7, 1.2 Hz, 6H, ArH), 5.8 (d, *J* = 4.0 Hz, 2H, CH_2OCH$_2$CH$_3$), 3.9 (q, *J* = 7.0 Hz, 2H, CH$_2$OCH_2CH$_3$), 1.1 (t, *J* = 7.0 Hz, 3H, CH$_2$OCH$_2$CH_3). ^{31}P NMR (122 MHz, $CDCl_3$) δ 18.6.

Analytical data in accordance with literature.[335]

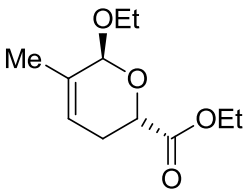
Synthesis of (*1E,3E*)-1-ethoxypenta-1,3-diene 131.2



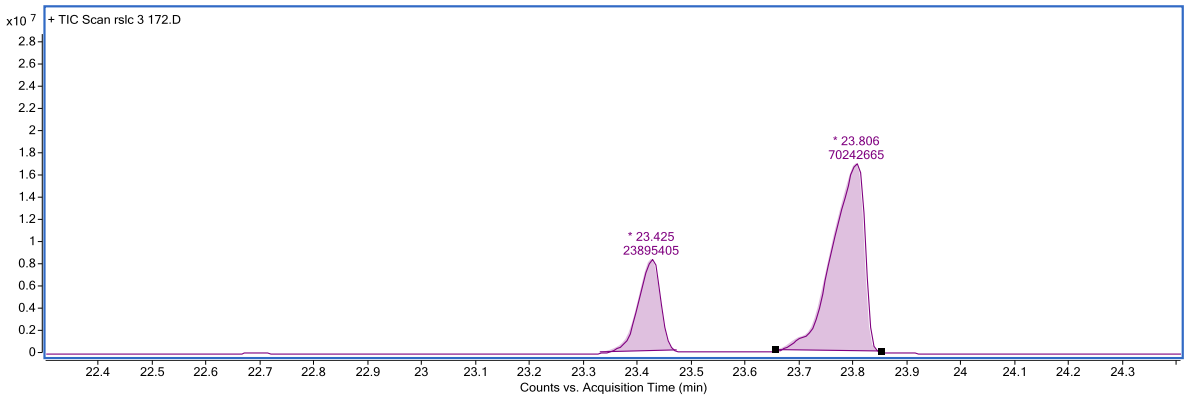
nBuLi (14.7 mL, 1.4 M in hexanes) was added slowly to a stirred solution of diisopropylamine (4.16 mL, 28.8 mmol) in THF (50 mL) at -78 °C and stirred for 10 min. The reaction was then warmed to 0 °C followed by the addition of (ethoxymethyl)triphenylphosphonium chloride (8.92 g, 25.0 mmol) the reaction was then allowed to warm to rt and stirred for 1 h. Freshly distilled crontonaldehyde (1.44 g, 20.6 mmol) was added dropwise and stirred for 2 h. The reaction was then diluted with H_2O (100 mL) and extracted with Et_2O (3x 50 mL), the combined organic layers were dried ($MgSO_4$) and carefully concentrated *in vacuo* to give a crude mixture of product and triphenylphosphine oxide. The product was purified by distillation under reduced pressure to give the title compound as a clear oil (1.73 g, 75%, 15.45 mmol). As a mixture of (*E, E*) and (*E, Z*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.5 – 6.4 (m, 1H), 6.4 (dddt, *J* = 12.6, 2.7, 1.8, 1.0 Hz, 1H), 6.0 – 5.9 (m, 1H), 5.9 – 5.8 (m, 1H), 5.6 – 5.4 (m, 3H), 5.0 (dd, *J* = 10.8, 6.2 Hz, 1H), 3.8 (dq, *J* = 21.3, 7.1 Hz, 4H), 1.8 – 1.7 (m, 6H), 1.3 (t, *J* =

7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 144.1, 127.4, 125.6, 124.3, 123.5, 106.9, 106.8, 68.2, 65.3, 18.4, 18.3, 15.4, 14.9.

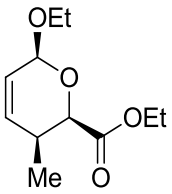
Synthesis of ethyl 6-ethoxy-5-methyl-3,6-dihydro-2H-pyran-2-carboxylate 132.2



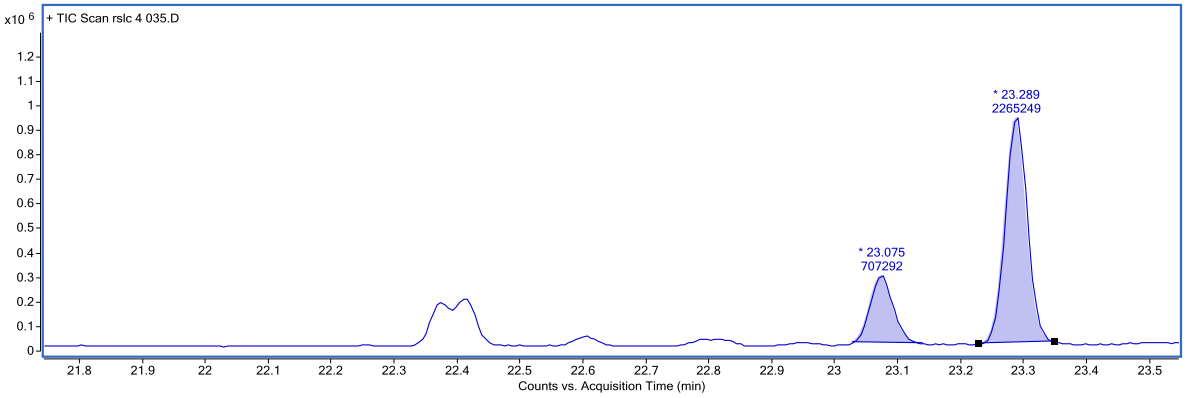
CH_2Cl_2 (3.0 mL) was added to binaphthol-titanium complex **106.3** (0.016 g, 0.04 mmol) under a N_2 environment, ethyl glyoxalate 50% in CH_2Cl_2 (0.32 mL, 1.6 mmol) was added and the reaction cooled to -30 °C. (*1E,3E*)-1-ethoxypenta-1,3-diene (0.09 g, 0.8 mmol) was added and the reaction was stirred at -30 °C for 4 h. The reaction was concentrated *in vacuo* to give a crude mixture which was purified by column chromatography (10% EtOAc in pentane Rf = 0.45). The fractions containing product were combined and concentrated *in vacuo* to give the title compound as a clear oil (0.116 g, 68%), $[\alpha]_D^{20}$ = +88 (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.6 (ddddd, *J* = 3.7, 2.8, 2.2, 1.5, 0.7 Hz, 1H, C=C*H*), 4.9 (s, 1H, OC*H*OCH_2CH_3), 4.5 – 4.4 (m, 1H, C*H*C(O)OCH_2CH_3), 4.2 (qd, *J* = 7.1, 3.2 Hz, 2H, CHC(O)O*C*H_2CH_3), 3.9 (dq, *J* = 9.9, 7.1 Hz, 1H, O*C*$H_aH_bCH_3$), 3.6 (dq, *J* = 9.8, 7.0 Hz, 1H, $OCH_aH_bCH_3$), 2.3 – 2.2 (m, 2H, C=CHCH_2), 1.7 (q, *J* = 2.0 Hz, 3H, CH_3C=C), 1.3 (t, *J* = 7.1 Hz, 3H, CHC(O)OCH_2CH_3), 1.2 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 132.7, 121.5, 97.9, 65.9, 64.2, 61.2, 27.9, 19.1, 15.4, 14.4. I.R (thin film) ν max (cm^{-1}): 2977, 2897 (C-H), 1736 (C=O). HRMS (ESI): m/z calculated. $C_{11}H_{18}O_4$: requires 237.1103 for $[M+Na]^+$; found: 237.1168.



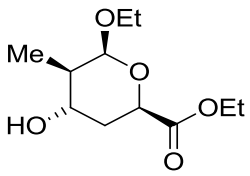
Synthesis of ethyl 6-ethoxy-3-methyl-3,6-dihydro-2H-pyran-2-carboxylate 133.1



CH_2Cl_2 (3.0 mL) was added to binaphthol-titanium complex **106.3** (0.016 g, 0.04 mmol) under a N_2 environment, ethyl glyoxalate 50% in CH_2Cl_2 (0.32 mL, 1.6 mmol) was added and the reaction cooled to -30 °C. (*E*)-1-ethoxy-2-methylbuta-1,3-diene (0.09 g, 0.8 mmol) was added and the reaction was stirred at -30 °C for 4 h. The reaction was concentrated *in vacuo* to give a crude mixture which was purified by column chromatography (10% EtOAc in pentane Rf = 0.45). The fractions containing product were combined and concentrated *in vacuo* to give the title compound as a clear oil (0.094 g, 55%), $[\alpha]_D^{20}$ = +73 (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.0 (ddd, *J* = 10.1, 5.3, 1.5 Hz, 1H, CH=C*H*CHCH$_3$), 5.6 (dt, *J* = 10.1, 1.2 Hz, 1H, C*H*=CHCHCH$_3$), 5.2 (dt, *J* = 2.6, 1.4 Hz, 1H, OC*H*OCH$_2$CH$_3$), 4.4 (d, *J* = 3.5 Hz, 1H, C*H*C(O)OCH$_2$CH$_3$), 4.3 (qd, *J* = 7.1, 1.0 Hz, 2H, CHC(O)OC*H*$_2$CH$_3$), 4.0 (dq, *J* = 9.4, 7.1 Hz, 1H, OC*H*$_a$H$_b$CH$_3$), 3.6 (dq, *J* = 9.4, 7.1 Hz, 1H, OC*H*$_a$H$_b$CH$_3$), 2.6 – 2.4 (m, 1H, C*H*CH$_3$), 1.3 (t, *J* = 7.2 Hz, 3H, CHC(O)OCH$_2$C*H*$_3$), 1.2 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH$_3$), 1.0 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 134.6, 126.7, 98.5, 74.0, 63.8, 61.1, 31.7, 15.4, 14.8, 14.4. I.R (thin film) $_v$max (cm^{-1}): 2977, 2897 (C-H), 1759 (C=O), 1731 (C=C). HRMS (ESI): m/z calculated. $C_{11}H_{18}O_4$: requires 237.1103 for $[M+Na]^+$; found: 237.1138.

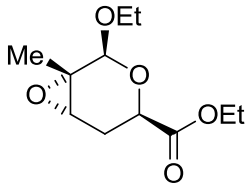


Synthesis of ethyl 6-ethoxy-4-hydroxy-5-methyltetrahydro-2H-pyran-2-carboxylate 134.1



Borane dimethyl sulfide complex (0.2 mL, 1.75 mmol) was added dropwise to a stirred solution of ethyl 6-ethoxy-5-methyl-3,6-dihydro-2H-pyran-2-carboxylate (0.18 g, 0.87 mmol) in THF (5 mL) at -5 °C the reaction was then placed in a freezer at -20 °C for 16 h. The reaction was warmed to -5 °C followed by the addition of H_2O_2 (30 % w/w) (0.548 mL) and NaOH (0.2 g, 4.35 mmol) the reaction was stirred for a further 1 h. The reaction was diluted with H_2O (10 mL) and Et_2O (20 mL) the layers were separated and the organics were washed with H_2O (3x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified *via* column chromatography (20% EtOAc in pentane, Rf = 0.35) the fractions containing product were combined and concentrated *in vacuo* to give the title compound as a clear oil (0.131 g, 65%). $[\alpha]_D^{20}$ = +63.5 (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.8 (d, *J* = 2.8 Hz, 1H), 4.4 (dd, *J* = 7.0, 4.5 Hz, 1H), 4.3 – 4.0 (m, 2H), 4.0 (td, *J* = 6.7, 3.7 Hz, 1H), 3.9 (dq, *J* = 9.7, 7.1 Hz, 1H), 3.5 (dq, *J* = 9.7, 7.1 Hz, 1H), 2.2 (ddd, *J* = 13.5, 7.2, 3.7 Hz, 1H), 1.9 – 1.7 (m, 2H), 1.3 (t, *J* = 7.1 Hz, 3H), 1.2 (t, *J* = 7.1 Hz, 3H), 1.0 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 101.2, 70.4, 68.3, 65.0, 61.2, 41.3, 32.8, 15.0, 14.3, 11.4. I.R (thin film) ν max (cm^{-1}): 3466 (OH), 2979, 2933 (C-H), 1736 (C=O). HRMS (ESI): m/z calculated. $C_{11}H_{20}O_5$: requires 255.12084 for $[M+Na]^+$; found: 255.1233.

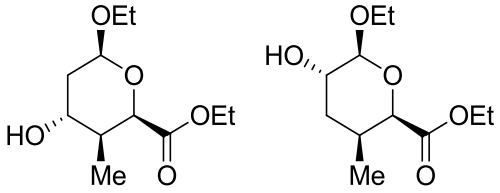
Synthesis of ethyl 2-ethoxy-1-methyl-3,7-dioxabicyclo[4.1.0]heptane-4-carboxylate 135.1/135.2



Ethyl 6-ethoxy-5-methyl-3,6-dihydro-2H-pyran-2-carboxylate (0.18 g, 0.87 mmol) was added to a mixture of $[(C_8H_{17})_3NCH_3]_3PO_4[W(O)(O_2)_2]_4$ (0.028 g, 0.0087 mmol) in 30% H_2O_2 (0.155 mL, 0.96 mmol) neutralised with 1 drop of 2M NaOH. The reaction was stirred at rt for 4 h. The reaction was diluted with $NaHCO_{3(aq)}$ (20 mL) and a Et_2O/Pentane mix (10 mL 1:1). The layers were separated and the aqueous layer is further extracted with Et_2O/Pentane 1:1 mix (3x 10 mL). The organic layers were then combined, dried ($MgSO_4$) and concentrated under vacuum to give pure title compound as a colourless oil in a 80% yield (0.160 g, 0.69 mmol). $[\alpha]_D^{20}$ = +61

(MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.8 (s, 1H), 4.3 – 4.1 (m, 3H), 4.0 (dq, *J* = 9.6, 7.1 Hz, 1H), 3.6 (dqd, *J* = 9.6, 7.0, 4.4 Hz, 1H), 3.3 – 3.1 (m, 1H), 2.3 (ddd, *J* = 14.7, 5.2, 2.5 Hz, 1H), 2.3 – 2.1 (m, 2H), 1.3 (d, *J* = 2.0 Hz, 3H), 1.3 (t, *J* = 7.1 Hz, 3H), 1.3 – 1.2 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 99.8, 98.0, 66.9, 65.3, 61.3, 56.9, 27.0, 18.2, 15.1, 14.2. I.R (thin film) ν max (cm^{-1}): 2979, 2932 (C-H), 1756 (C=O). HRMS (ESI): m/z calculated. $C_{12}H_{20}O_5$: requires: 245.1388 for $[M+H]^+$; found: 245.1378.

Synthesis of ethyl 6-ethoxy-4-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate and ethyl 6-ethoxy-5-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate 136.1/136.2



Borane dimethyl sulfide complex (0.22 mL, 1.86 mmol) was added dropwise to a stirred solution of ethyl 6-ethoxy-5-methyl-3,6-dihydro-2H-pyran-2-carboxylate (0.20 g, 0.93 mmol) in THF (5 mL) at -5 °C the reaction was then placed in a freezer at -20 °C for 16 h. The reaction was warmed to -5 °C followed by the addition of H_2O_2 (30 % w/w) (0.548 mL) and NaOH (0.2 g, 4.35 mmol) the reaction was stirred for a further 1 h. The reaction was diluted with H_2O (10 mL) and Et_2O (20 mL) the layers were separated and the organics were washed with H_2O (3x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified *via* column chromatography (20% EtOAc in pentane, Rf = 0.37 and 0.35). The fractions containing product were combined and concentrated *in vacuo* to give ethyl 6-ethoxy-4-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate as a clear oil (0.097 g, 45%) and ethyl 6-ethoxy-5-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate as a mix of diastereomers (0.064 g, 30%).

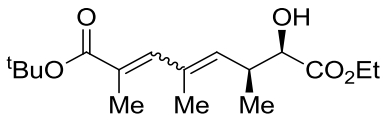
Ethyl 6-ethoxy-4-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate 136.1

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.3 – 4.2 (m, 2H, C(O)OCH_2CH$_3$), 4.2 (d, *J* = 2.7 Hz, 1H, CHOCH$_2$CH$_3$), 4.2 (d, *J* = 7.7 Hz, 1H, CHC(O)OCH$_2$CH$_3$), 4.1 (dq, *J* = 10.2, 7.3 Hz, 1H, OCH_aH$_b$CH$_3$), 3.7 (ddd, *J* = 12.3, 7.7, 5.1 Hz, 1H, CHOH), 3.6 – 3.5 (m, 1H, OCH$_a$$H_bCH_3$), 2.4 (qdt, *J* = 7.4, 5.1, 2.6 Hz, 1H, CHCH$_3$), 2.0 (ddd, *J* = 13.1, 5.1, 2.3 Hz, 1H, CH_aH$_b$CHOH), 1.8 – 1.7 (m, 1H, CH$_a$$H_b$CHOH), 1.3 – 1.3 (m, 3H, C(O)OCH$_2$CH_3), 1.3 – 1.2 (m, 3H, CHOCH$_2$CH_3), 1.0 (d, *J* = 7.2 Hz, 3H, CHCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 106.0, 77.1, 65.9, 65.4, 61.1, 36.4, 31.9, 15.2, 14.4, 13.9. I.R (thin film) ν max (cm^{-1}): 3484 (OH), 2976, 2934 (C-H), 1735 (C=O). HRMS (ESI): m/z calculated. $C_{11}H_{20}O_5$: requires: 255.12084 for [M+Na]; found: 255.1219.

Ethyl 6-ethoxy-5-hydroxy-3-methyltetrahydro-2H-pyran-2-carboxylate 136.2

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.3 – 4.2 (m, 2H, C*H*OCH_2CH_3 and C*H*C(O)OCH_2CH_3), 4.0 – 3.8 (m, 1H, C*H*OH), 3.6 – 3.5 (m, 2H, C(O)OC*H*$_2CH_3$), 3.4 (dt, *J* = 9.4, 3.0 Hz, 1H, C*H*$_a$H$_b$CH$_3$), 3.3 (ddd, *J* = 9.4, 7.9, 3.4 Hz, 1H, CH$_a$*H*$_b$CH$_3$), 2.3 (dtdt, *J* = 12.1, 7.5, 5.2, 2.6 Hz, 1H, C*H*CH$_3$), 1.7 – 1.5 (m, 1H, C*H*$_a$H$_b$CHOH), 1.5 – 1.4 (m, 1H, CH$_a$*H*$_b$CHOH), 1.3 (td, *J* = 7.1, 2.2 Hz, 3H, C(O)OCH_2CH_3), 1.2 (td, *J* = 7.0, 0.8 Hz, 3H, $CHOCH_2CH_3$), 0.9 (dd, *J* = 6.9, 2.3 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 110.2, 75.4, 75.1, 74.3, 72.4, 68.6, 67.7, 66.9, 66.8, 61.9, 61.8, 36.7, 36.5, 33.8, 33.2, 15.3, 14.4, 14.1, 13.2. I.R (thin film) ν max (cm^{-1}): 3466 (OH), 2971, 2932 (C-H), 1737 (C=O). HRMS (ESI): m/z calculated. $C_{11}H_{20}O_5$: requires: 255.12084 for [M+Na]; found: 255.1260.

Synthesis of 1-tert-butyl 8-ethyl 7-hydroxy-2,4,6-trimethylocta-2,4-dienedioate 138.2



5 M HCl (1.2 mL in 0.4 mL of H_2O) was added to a stirred solution of (2R,3S,6S)-ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (0.20 g, 0.8 mmol) in THF (10 mL) at rt. The reaction was heated to 50 °C and heated for 1.5 h. the reaction was cooled and quenched with $NaHCO_3$(aq) (10 mL). The reaction was extracted with Et_2O (3x 30 mL) and the organics were combined, dried ($MgSO_4$) and concentrated *en vacuo* to give the synthetic sugar. The material was carried forward as the crude product for the next step. The residue was dissolved in toluene (5 mL) and stirred at rt. To this was added benzoic acid (0.005 g, 0.04 mmol) and tert-butyl 2-(triphenylphosphoranylidene)propanoate (0.344 g, 0.88 mmol). The reaction was heated to reflux and stirred for 8 h. The reaction was then cooled and concentrated, the resulting residue was purified by column chromatography (20% EtOAc in pet ether Rf = 0.2) to give the title compound as a pale yellow wax in a 70% yield (0.175 g, 0.56 mmol) as a mixture of E/Z isomers.

E isomer

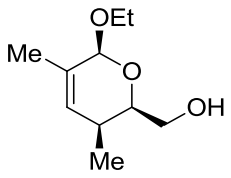
^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.1 (d, *J* = 1.9 Hz, 1H, ($CO_2{}^t$Bu)C=C*H*C=CH), 5.4 (dq, *J* = 10.2, 1.5 Hz, 1H, ($CO_2{}^t$Bu)C=CHC=C*H*), 4.3 – 4.2 (m, 2H, C*H*$_2CH_3$), 4.0 (dd, *J* = 6.3, 3.7 Hz, 1H, C*H*OH), 2.8 – 2.6 (m, 1H, C*H*CH$_3$), 1.8 (s, 3H, ($CO_2{}^t$Bu)C*H*$_3$C=C-(CH$_3$)C=C), 1.8 (d, *J* = 1.4 Hz, 3H, ($CO_2{}^t$Bu)CH$_3$C=C-(C*H*$_3$)C=C), 1.5 (s, 9H, C(C*H*$_3$)$_3$), 1.3 – 1.3 (m, 3H, CH_2CH_3), 0.9 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$).

Z isomer

^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.1 – 7.0 (m, 1H, ($CO_2{}^t$Bu)C=C*H*C=CH), 5.5 (d, *J* = 9.8 Hz, 1H, ($CO_2{}^t$Bu)C=CHC=C*H*), 4.4 – 4.2 (m, 2H, C*H*$_2$CH$_3$), 4.1 (dd, *J* = 6.4, 4.1 Hz, 1H, C*H*OH), 3.0 – 2.9 (m, 1H, C*H*CH$_3$), 2.0 (d, *J* = 1.5 Hz, 3H, ($CO_2{}^t$Bu)C*H*$_3$C=C-(CH$_3$)C=C), 1.9 (d, *J* = 1.4 Hz, 3H, ($CO_2{}^t$Bu)CH$_3$C=C-(C*H*$_3$)C=C), 1.5 (s, 3H, C(C*H*$_3$)$_3$), 1.3 (dd, *J* = 7.1, 5.4 Hz, 3H, CH$_2$C*H*$_3$), 1.0 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$).

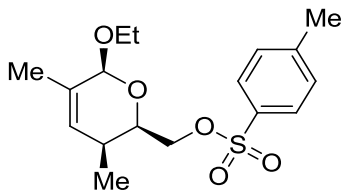
^{13}C NMR (75 MHz, Chloroform-*d*) δ 174.4, 168.4, 167.7, 141.5, 137.7, 135.5, 133.1, 132.8, 131.4, 130.3, 130.1, 128.0, 80.5, 80.3, 74.1, 74.0, 62.0, 61.8, 37.5, 37.2, 28.3, 23.3, 16.8, 14.9, 14.5, 14.4, 14.3, 14.3, 14.2. I.R (thin film) $_{\nu}$max (cm^{-1}): 3497 (OH), 2977, 2933 (C-H), 1730, 1702 (C=O). HRMS (ESI): m/z calculated. $C_{17}H_{28}O_5$: requires 313.20149 for $[M]^+$; found: 313.2001.

6-Ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)methanol 137.1



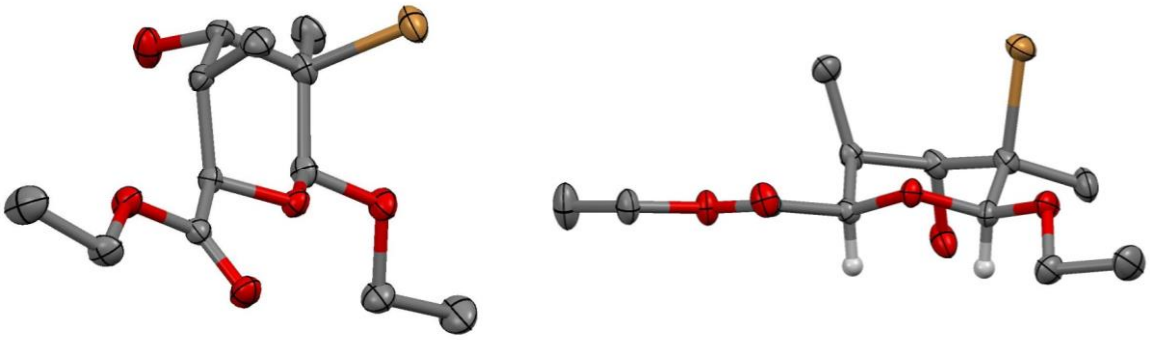
$LiAlH_4$ (2.4 M in THF, 4.0 mL) was added dropwise to a solution of (2R,3S,6S)-ethyl 6-ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-carboxylate (1.0 g, 4.8 mmol) in THF (10 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and then poured into a solution of saturated NH_4Cl (20 mL). The reaction mixture was then extracted with Et_2O (3x 30 mL) and the organics were combined, dried ($MgSO_4$) and concentrated *en vacuo* to give pure title compound as a clear oil in 95% yield (0.85 g, 4.56 mmol). $[\alpha]_D{}^{20}$ = +71 (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.6 (dp, *J* = 4.4, 1.5 Hz, 1H, C=C*H*), 4.9 (dt, *J* = 2.0, 1.0 Hz, 1H, C*H*CH$_2$CH$_3$), 3.9 – 3.8 (m, 2H, CHC*H*$_2$CH$_3$), 3.8 – 3.5 (m, 2H, CHC*H*$_2$OH), 2.5 (br s, 1H, C*H*CH$_2$OH), 2.4 (tdd, *J* = 7.1, 3.9, 2.0 Hz, 1H, C*H*CH$_3$), 1.7 (td, *J* = 1.8, 0.9 Hz, 3H, C=CC*H*$_3$), 1.3 (t, *J* = 7.1 Hz, 3H, CHCH$_2$C*H*$_3$), 1.0 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 129.7, 98.4, 75.3, 63.8, 63.1, 30.8, 18.3, 15.4, 14.8. I.R (thin film) $_{\nu}$max (cm^{-1}): 3423 (OH), 2970, 2930, 2875 (C-H). HRMS (ESI): m/z calculated. $C_{10}H_{18}O_3$: requires 209.1153 for $[M+Na]^+$; found: 209.1162.

6-Ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate 141.1



NEt_3 (0.19 mL, 1.48 mmol) was added to a solution of 6-Ethoxy-3,5-dimethyl-3,6-dihydro-2H-pyran-2-yl)methanol (0.25 g, 1.34 mmol) and tosyl chloride (0.28 g, 1.48 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 16 h. The reaction was diluted with 1 M NaOH and extracted with Et_2O (3x 30 mL) and the organics were combined, dried ($MgSO_4$) and concentrated *en vacuo*, the resulting residue was purified by column chromatography (10% EtOAc in pet ether Rf = 0.4) to give the title compound as a clear oil in a 82% yield (0.374 g, 1.10 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.9 – 7.7 (m, 2H, Ar*H*), 7.4 – 7.3 (m, 2H, Ar*H*), 5.5 (dp, *J* = 4.5, 1.5 Hz, 1H, C=C*H*), 4.9 (s, 1H, C*H*OCH_2CH_3), 4.2 – 3.9 (m, 3H, C*H*CH_2OSO_2Ts and CHC*H*$_2OSO_2$Ts), 3.7 (dq, *J* = 9.5, 7.1 Hz, 1H, CHOC*H*$_a$H$_b$$CH_3$), 3.5 (dq, *J* = 9.6, 7.1 Hz, 1H, CHOCH$_a$*H*$_b$$CH_3$), 2.4 (s, 3H, C*H*$_3$Ar), 2.2 (dddt, *J* = 9.3, 5.8, 4.0, 2.1 Hz, 1H, C*H*CH_3), 1.6 (q, *J* = 1.3 Hz, 3H, C=CC*H*$_3$), 1.2 (td, *J* = 7.1, 2.3 Hz, 3H, CHOCH$_a$H$_b$C*H*$_3$), 0.9 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 144.0, 132.8, 130.0, 129.0, 128.1, 99.4, 71.9, 69.8, 63.4, 30.7, 21.8, 17.9, 15.3, 14.1. I.R (thin film) $_{\nu}$max (cm^{-1}): 2971, 2879 (C-H). HRMS (ESI): m/z calculated. $C_{17}H_{24}O_3S_1$: requires 363.1242 for $[M+Na]^+$; found: 363.1246.

X-Ray Crystallography Data



Name	rslc-2-127
Formula	C12 H21 Br O5
M / g mol^{-1}	325.20
T (K), radiation	150, Cu K_α
Space Group	$P2_1/c$
a (Å)	13.7446(2)
b (Å)	12.37620(10)
c (Å)	8.59960(10)
α (°)	90
β (°)	104.2950(10)
γ (°)	90
Volume ($Å^3$)	1417.55(3)
Z	4
ρ_{cal}/ Mg cm^{-3}	1.524
μ/mm^{-1}	4.067
θ range/°	4.878-66.601
Completeness	100 %
Refln. Collected	14324
Independent	2502
Refln (obs./>2σ(*I*))	2456
Rint	0.0234

Parameters	247
GooF	0.947
R_1 (obs)	0.0216
R_1 (all)	0.0219
wR_2 (all)	0.0585
$\rho_{max,min}$/e Å^{-3}	0.304,-0.338

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